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Body positioning for spontaneously breathing preterm infants with apnoea (Review)

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[Intervention Review]

Body positioning for spontaneously breathing preterm infants with apnoea

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ABSTRACT

Background

It has been proposed that body positioning in preterm infants, as compared with other, more invasive measures, may be an effective method of reducing clinically significant apnoea.

Objectives

To determine effects of body positioning on cardiorespiratory parameters in spontaneously breathing preterm infants with clinically significant apnoea.

Subgroup analyses examined effects of body positioning of spontaneously breathing preterm infants with apnoea from the following subgroups.

• Gestational age < 28 weeks or birth weight less than 1000 grams.

• Apnoea managed with methylxanthines.

• Frequent apnoea (> 10 events/d).

• Type of apnoea measured (central vs mixed vs obstructive)

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group (CNRG) to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10), MEDLINE via PubMed (1966 to 14 November 2016), Embase (1980 to 14 November 2016) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 2016 November 14). We also searched clinical trials databases and conference proceedings for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised and quasi-randomised controlled clinical trials with parallel, factorial or cross-over design comparing the impact of different body positions on apnoea in spontaneously breathing preterm infants were eligible for our review.

Data collection and analysis

We assessed trial quality, data extraction and synthesis of data using standard methods of the CNRG. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.

Main results

The search conducted in November 2016 identified no new studies. Five studies (N = 114) were eligible for inclusion. None of the individual studies nor meta-analyses showed a reduction in apnoea, bradycardia, oxygen desaturation or oxygen saturation with body positioning (supine vs prone; prone vs right lateral; prone vs left lateral; right lateral vs left lateral; prone horizontal vs prone head elevated; right lateral horizontal vs right lateral head elevated, left lateral horizontal vs left lateral head elevated).

Authors' conclusions

We found insufficient evidence to determine effects of body positioning on apnoea, bradycardia and oxygen saturation in preterm infants. No new studies have been conducted since the original review was published. Large, multi-centre studies are warranted to provide conclusive evidence, but it may be plausible to conclude that positioning of spontaneously breathing preterm infants has no effect on their cardiorespiratory parameters.

PLAIN LANGUAGE SUMMARY

Body position and apnoea in the preterm infant

Review question: Does body positioning affect cardiorespiratory parameters in spontaneously breathing preterm infants with clinically significant apnoea?

Background: Apnoea is a condition in which an infant stops breathing for a short duration but then resumes normal breathing. Apnoea is rare among infants born at term, but its incidence increases with decreasing gestational age. Apnoea is generally considered a normal occurrence in the healthy preterm infant. However, long-term consequences of recurrent apnoea that lead to lower oxygen levels in sick preterm infants remain unknown. In addition, little agreement has been reached about what degree of apnoea is acceptable. It has been proposed that body positioning is an easy, practical and effective intervention as compared with other, invasive measures for minimising or preventing apnoea. Therefore, this review was conducted to see if different body positions can prevent or alleviate apnoea.

Study characteristics: Review authors searched the medical literature and identified five eligible trials that recruited a total of 114 infants. Our updated search (November 2016) identified no new studies for inclusion in this review. Included studies examined effects on cardiorespiratory parameters of supine versus prone; prone versus right lateral; prone versus left lateral; right lateral versus left lateral; prone horizontal versus prone head elevated; right lateral horizontal versus right lateral head elevated; and left lateral horizontal versus left lateral head elevated positions in spontaneously breathing preterm infants with apnoea.

Key results: None of the individual included studies nor meta-analyses showed differences on cardiorespiratory parameters between different preterm infant body positions.

Quality of evidence: The overall quality of evidence was low to very low because of high or unclear risk of bias and imprecise results yielded by small sample sizes. Thus, this review cannot recommend use of one body position over another for spontaneously breathing preterm infants with apnoea.

Summary of findings for the main comparison. Supine versus prone positioning

Supine versus prone positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care
Intervention: supine positioning
Comparison: prone positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with prone positioning	Risk with supine positioning			
Episodes of apnoea	**Mean difference (MD)** 1.09 (-0.65 to 2.82) Favours prone positioning group *Not statistically significant*		Overall, episodes of apnoea were 1.09 more (0.65 fewer to 2.82 more) among preterm infants in the supine positioning group compared with preterm infants in the prone positioning group.	72 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]
Episodes of oxygen desaturation	**Mean difference (MD)** 0.8 (-3.19 to 4.79) Favours prone positioning group *Not statistically significant*		Overall, episodes of oxygen desaturation were 0.8 more (3.19 fewer to 4.79 more) among preterm infants in the supine positioning group compared with preterm infants in the prone positioning group..	44 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of bradycardia	**Mean difference (MD)** 0.13 (-3.2 to 2.94) Favours supine positioning group *Not statistically significant*		Overall, episodes of bradycardia were 0.13 fewer (3.2 fewer to 2.94 more) among preterm infants in the supine positioning group compared with preterm infants in the prone positioning group.	72 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.
[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Imprecision: broad confidence interval.
[e]Single study.

Summary of findings 2. Prone horizontal versus right lateral horizontal positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care
Intervention: prone horizontal positioning
Comparison: right lateral horizontal positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with right lateral horizontal positioning	Risk with prone horizontal positioning			
Episodes of apnoea	**Mean difference (MD)** 0.48 (-0.19 to 1.15) Favours right lateral horizontal positioning group *Not statistically significant*		Overall, episodes of apnoea were 0.48 more (0.19 fewer to 1.15 more) among preterm infants in the prone horizontal positioning group compared preterm infants in the right lateral horizontal positioning group.	130 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c,d]

Episodes of oxygen desaturation	**Mean difference (MD)** -1.86 (-4.29 to 0.56) Favours prone horizontal positioning group *Not statistically significant*	Overall, episodes of oxygen desaturation were 1.86 fewer (4.29 fewer to 0.56 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the right lateral horizontal positioning group.	88 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe apnoea	**Mean difference (MD)** 0.05 (-0.45 to 0.54) Favours right lateral horizontal positioning group *Not statistically significant*	Overall, episodes of severe apnoea were 0.05 more (0.45 fewer to 0.54 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the right lateral horizontal positioning group.	88 (1 RCT)	⊕⊖⊖⊖ Very low[a.b.c.d]
Episodes of bradycardia	**Mean difference (MD)** -0.59 (-2.4 to 1.23) Favours prone horizontal positioning group *Not statistically significant*	Overall, episodes of bradycardia were 0.59 fewer (2.41 fewer to 1.23 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the right lateral horizontal positioning group.	88 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe bradycardia	**Mean difference (MD)** - 0.32 (-1.02 fewer to 0.39) Favours prone horizontal positioning group *Not statistically significant*	Overall, episodes of severe bradycardia were 0.32 fewer (1.02 fewer to 0.39 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the right lateral horizontal positioning group.	88 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to that the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.
[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Single study.
[e]Imprecision: broad confidence interval.

Summary of findings 3. Prone horizontal versus left lateral horizontal positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care
Intervention: prone horizontal positioning
Comparison: left lateral horizontal positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with left lateral horizontal positioning	Risk with prone horizontal positioning			
Episodes of apnoea	**Mean difference (MD)** 0.2 (-0.75 to 1.15) Favours left lateral horizontal positioning *Not statistically significant*		Overall, episodes of apnoea were 0.2 more (0.75 fewer to 1.15 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the left lateral horizontal positioning group.	131 (2 RCTs)	⊕⊕⊖⊖ Low[a,b,c]
Episodes of oxygen desaturation	**Mean difference (MD)** -1.44		Overall, episodes of oxygen desaturation were 1.44 fewer (3.81 fewer to 0.92 more) among preterm infants in the prone horizontal positioning group compared	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]

	(-3.81 to 0.92) Favours prone horizontal positioning *Not statistically significant*	with preterm infants in the lateral horizontal positioning group.		
Episodes of severe apnoea	**Mean difference (MD)** 0.11 (-0.38 to 0.6) Favours left lateral horizontal positioning *Not statistically significant*	Overall, episodes of severe apnoea were 0.11 more (0.38 fewer to 0.6 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the left lateral horizontal positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,e]
Episodes of bradycardia	**Mean difference (MD)** - 0.17 (-0.94 to 0.6) Favours prone horizontal positioning group *Not statistically significant*	Overall, episodes of bradycardia were 0.17 fewer (0.94 fewer to 0.49 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the left lateral horizontal positioning group (0.94 less to 0.6 more frequent).	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,e]
Episodes of severe bradycardia	**Mean difference (MD)** -0.22 (-0.94 to 0.49) Favours prone horizontal positioning group *Not statistically significant*	Overall, episodes of severe bradycardia were 0.22 fewer (0.94 fewer to 0.49 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the left lateral horizontal positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.

[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Imprecision: broad confidence interval.
[e]Single study.

Summary of findings 4. Right lateral versus left lateral positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care
Intervention: right lateral positioning
Comparison: left lateral positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with left lateral positioning	Risk with right lateral positioning			
Episodes of apnoea	**Mean difference (MD)** -0.27 (-1.1 to 0.57) Favours right lateral positioning *Not statistically significant*		Overall, episodes of apnoea were 0.27 fewer (1.1 fewer to 0.57 more) among preterm infants in the right lateral positioning group compared with preterm infants in the left lateral positioning group.	131 (2 RCTs)	⊕⊕⊖⊖ Low[a,b,c]
Episodes of oxygen desaturation	**Mean difference (MD)** 0.42 (-2.42 to 3.26) Favours left lateral positioning *Not statistically significant*		Overall, episodes of oxygen desaturation were 0.42 more (2.42 fewer to 3.26 more) among preterm infants in the right lateral positioning group compared with preterm infants in the left lateral positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,,d,e]
Episodes of severe apnoea	**Mean difference (MD)** 0.01 (-0.4 to 0.42) Favours left lateral positioning		Overall, episodes of severe apnoea were 0.01 more (0.4 fewer to 0.42 more) among preterm infants in the right lateral positioning group compared with preterm infants in the left lateral positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,e]

	Not statistically significant			
Episodes of bradycardia	**Mean difference (MD)** 0.42 (-1.43 to 2.27) Favours left lateral positioning *Not statistically significant*	Overall, episodes of bradycardia in the intervention group were 0.42 more (1.43 fewer to 2.27 more) among preterm infants in the right lateral positioning group compared with preterm infants in the left lateral positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe bradycardia	**Mean difference (MD)** 0.09 (-0.68 to 0.87) Favours left lateral positioning *Not statistically significant*	Overall, episodes of severe bradycardia were 0.09 more (0.68 fewer to 0.87 more) among preterm infants in the right lateral positioning group compared with preterm infants in the left lateral positioning group.	89 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.
[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Imprecision: broad confidence interval.
[e]Single study.

Summary of findings 5. Prone horizontal versus prone head elevated positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care

Intervention: prone horizontal positioning
Comparison: prone head elevated positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with prone head elevated positioning	Risk with prone horizontal positioning			
Episodes of apnoea	**Mean difference (MD)** -0.18 fewer (-1.09 to 0.73) Favours prone horizontal positioning *Not statistically significant*		Overall, episodes of apnoea were 0.18 fewer (1.09 fewer to 0.73 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the prone head elevated positioning group.	129 (2 RCTs)	⊕⊕⊖⊖ Low[1,3,4]
Episodes of oxygen desaturation	**Mean difference (MD)** -0.62 (-2.81 to 1.56) Favours prone horizontal positioning *Not statistically significant*		Overall, episodes of oxygen desaturation were 0.62 fewer (2.81 fewer to 1.56 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the prone head elevated positioning group.	111 (2 RCTs)	⊕⊖⊖⊖ Very low[1,2,3,4]
Episodes of severe apnoea	**Mean difference (MD)** -0.24 (-0.83 to 0.35) Favours prone horizontal positioning *not statistically significant*		Overall, episodes of severe apnoea were 0.24 fewer (0.83 fewer to 0.35 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the prone head elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[1,3,4,5]
Episodes of bradycardia	**Mean difference (MD)** -0.14 (-1.03 to 0.74) Favours prone horizontal positioning *not statistically significant*		Overall, episodes of bradycardia were 0.14 fewer (1.03 fewer to 0.74 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the prone head elevated positioning group.	111 (2 RCTs)	⊕⊕⊖⊖ Low[1,3,4]

Episodes of severe bradycardia	**Mean difference (MD)** -0.28 (-1.15 to 0.59) Favours prone horizontal positioning *not statistically significant*	Overall, episodes of severe bradycardia were 0.28 fewer (1.15 fewer to 0.59 more) among preterm infants in the prone horizontal positioning group compared with preterm infants in the prone head elevated positioning group.	111 (2 RCTs)	⊕⊕⊖⊖ Low[1,3,4]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]High risk or unclear allocation concealment
[2] Imprecision: broad confidence interval
[3] High risk or unclear risk performance bias
4 High risk or unclear risk detection bias
5 Single study

Summary of findings 6. Right lateral horizontal versus right lateral elevated positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: Prone horizontal
Intervention: Right lateral horizontal positioning
Comparison: right lateral elevated positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with right lateral elevated positioning	Risk with Right lateral horizontal positioning			

Episides of apnoea	**Mean difference (MD)** -0.79 (-2.26 to 0.69) Favours right lateral horizontal positioning group *not statistically significant*	Overall, episodes of apnoea were 0.79 fewer (2.26 fewer to 0.69 more) in preterm infants in the right lateral horizontal positioning group compared with preterm infants in the right lateral elevated positioning group.	86 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]
Episodes of oxygen desaturation	**Mean difference (MD)** 0.03 (-3.06 to 3.11) Favours right lateral elevated positioning group *not statistically significant*	Overall, episodes of oxygen desaturation were 0.03 more (3.06 fewer to 3.11 more) in preterm infants in the right lateral horizontal positioning group compared with preterm infants in the right lateral elevated positioning group.	86 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe apnoea	**Mean difference (MD)** -0.14 (-0.69 to 0.41) Favours right lateral horizontal positioning group *not statistically significant*	Overall, episodes of severe apnoea were 0.14 fewer (0.69 fewer to 0.41 more) in preterm infants in the right lateral horizontal positioning group compared with preterm infants in the right lateral elevated positioning group.	86 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]
Episodes of bradycardia	**Mean difference (MD)** 0.34 (-1.54 to 2.22) Favours right lateral elevated positioning group *not statistically significant*	Overall, episodes of bradycardia were 0.34 more (1.54 fewer to 2.22 more) in preterm infants in the right lateral horizontal positioning group compared with preterm infants in the right lateral elevated positioning group.	86 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe bradycardia	**Mean difference (MD)** 0.6 (-0.25 to 1.46) Favours right lateral elevated positioning group *not statistically significant*	Overall, episodes of severe bradycardia were 0.6 more (0.25 fewer to 1.46 more) in preterm infants in the right lateral horizontal positioning group compared with preterm infants in the right lateral elevated positioning group.	86 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.
[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Single study.
[e]Imprecision: broad confidence interval.

Summary of findings 7. Left lateral horizontal versus left lateral elevated positioning

Patient or population: spontaneously breathing preterm infants with apnoea
Setting: neonatal/special care
Intervention: left lateral horizontal positioning
Comparison: left lateral elevated positioning

Outcomes	Anticipated absolute effects* (95% CI)		Comments	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with left lateral elevated positioning	Risk with left lateral horizontal positioning			
Episodes of apnoea	**Mean difference (MD)** 0.46 (-0.34 to 1.26) Favours left lateral elevated positioning group.		Overall, episodes of apnoea were 0.46 more (0.34 fewer to 1.26 more) among preterm infants in the left lateral horizontal positioning group compared with preterm infants in the left lateral elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]

	Not statistically significant			
Episodes of oxygen desaturation	**Mean difference (MD)** 0.63 (-2.09 to 3.35) Favours left lateral elevated positioning group. *Not statistically significant*	Overall, episodes of oxygen desaturation in the left lateral horizontal positioning were 0.63 times more (2.09 fewer to 3.35 more) among preterm infants in the left lateral horizontal positioning group compared with preterm infants in the left lateral elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]
Episodes of severe apnoea	**Mean difference (MD)** 0.18 (-0.18 to 0.54) Favours left lateral elevated positioning group. *Not statistically significant*	Overall, episodes of severe apnoea in the left lateral horizontal positioning group were 0.18 more (0.18 fewer to 0.54 more) among preterm infants in the left lateral horizontal positioning group compared with preterm infants in the left lateral elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]
Episodes of bradycardia	**Mean difference (MD)** 0.08 (-0.71 to 0.88) Favours left lateral elevated positioning group. *Not statistically significant*	Overall, episodes of bradycardia in the left lateral horizontal positioning group were 0.08 more (0.71 fewer to 0.88 more) among preterm infants in the left lateral horizontal positioning group compared with preterm infants in the left lateral elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]
Episodes of severe bradycardia	**Mean difference (MD)** -0.17 (-0.93 to 0.58) Favours left lateral horizontal positioning group. *Not statistically significant*	Overall, episodes of severe bradycardia in the left lateral horizontal positioning group were 0.17 fewer (0.93 fewer to 0.58 more) among preterm infants in the left lateral horizontal positioning group compared with preterm infants in the left lateral elevated positioning group.	87 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference.

GRADE Working Group grades of evidence.
High quality: We are very confident that the true effect lies close to the estimate of effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]High or unclear risk of allocation concealment.
[b]High or unclear risk of performance bias.
[c]High or unclear risk of detection bias.
[d]Single study.
[e]Imprecision: broad confidence interval.

BACKGROUND

Description of the condition

Apnoea of prematurity (AOP) is defined as a pause in breathing lasting at least 20 seconds on its own, or at least 10 seconds with concomitant bradycardia and/or hypoxaemia, that occurs in preterm infants (gestational age < 37 weeks) (Fairchild 2016; Zhao 2011). AOP reflects immaturity of the brainstem and peripheral chemoreceptors that results in an abnormal ventilatory response to high carbon dioxide (hypercarbia) and low oxygen (hypoxia), along with immature reflex responses (Fairchild 2016; Henderson-Smart 1981; Morton 2016; Zhao 2011). Apnoea can be classified as central, obstructive or mixed in type. Central apnoea has its origins in the central nervous system (CNS) and is characterised by absence of a respiratory effort. Obstructive apnoea, which is less common than central apnoea, is usually encountered only in infants with upper airway abnormalities (such as floppy tissue obstructing the airway) or in infants with rare brainstem anomalies such as Dandy-Walker malformations (Eichenwald 2016; Henderson-Smart 1995; Janvier 2004). Moreover, improper neck positioning, especially flexion, can cause airway obstruction in preterm infants that mimics obstructive apnoea. Mixed apnoea, the most common type among preterm infants, comprises components of both central apnoea and obstructive apnoea. Usually, mixed apnoeic episodes start as central apnoea that subsequently results in a decrease in upper airway tone, leading to obstruction and thus an obstructive apnoea-like mechanism that persists even when respiratory effort is resumed (Eichenwald 2016).

The incidence of AOP increases with decreasing gestational age and lower birth weight, and the condition affects 90% of infants born before 28 weeks of gestation or with birth weight less than 1000 grams. AOP is distinct from apnoea as witnessed in term infants. Term infants with apnoea are more likely to have a serious underlying condition that may account for their apnoea, such as infection, a neurological anomaly or a metabolic disorder (Morton 2016). Hypoxia associated with apnoea could have detrimental effects on the infant's developing tissues and organs, resulting in long-term or permanent impairment, such as retinopathy of prematurity (ROP), impaired growth, cardiorespiratory instability and impaired neurodevelopmental outcomes (Di Fiore 2010). Risk of hypoxaemic episodes is increased when peripheral capillary oxygen saturation (SpO_2) decreases to ≤ 80% or 85% for longer than 10 seconds (Janvier 2004; Morton 2016).

Managing AOP, determining optimal levels and durations of various therapies, and determining readiness of affected infants for discharge from the neonatal intensive care unit (NICU) continue to present major challenges, and accurate quantitation of apnoea is required for both appropriate clinical care and outcomes research (Butler 2014; Fairchild 2016). If an infant with AOP does not respond to tactile stimulation, interventions such as positioning, stochastic resonance, respiratory stimulants, oxygen therapy or ventilation may become necessary. However, treatment should start with efforts to identify and correct known conditions that can increase the likelihood of AOP such as hypoglycaemia, hypocalcaemia, metabolic alkalosis, anaemia, arterial hypotension and any condition that increases the workload of breathing. Medications that depress CNS activity also favour apnoea and should be avoided if possible.

Positioning

We found conflicting statements in the literature regarding which position is most appropriate for low birth weight (LBW) preterm infants. US national guidelines for prevention of sudden infant death syndrome (SIDS) recommend the supine position for preterm infants who are ready to be discharged (AAP 2003; Blair 2006). However, the preferred practice of neonatal nurses has long been to place preterm infants in the prone position when providing care to reduce stress (Ghorbani 2013; Candia 2014; Peng 2014), increase oxygenation and decrease episodes of desaturation (Balaguer 2013; Gillies 2012).

Stochastic resonance

A few studies have found that mechanosensory stimulation, also known as 'stochastic resonance', delivered through filtered low-amplitude white noise provided by actuators embedded within the infant's mattress, led to a decrease in the number, duration and intensity of oxygen desaturation events (Bloch-Salisbury 2009; Smith 2015), probably caused by improved breathing and attenuated inhibitory reflexes attained by stochastic vibrotactile stimulation (Waggener 1982).

Respiratory stimulants

When apnoeic episodes are severe and persistent, respiratory stimulants, namely, xanthines, such as caffeine, theophylline and aminophylline, can be used. Xanthines act centrally to cause brainstem stimulation, leading to an increased respiratory drive, enhanced sensitivity to hypercarbia and reduced tolerance to hypoxia (Morton 2016). Although these respiratory stimulants are similarly effective in alleviating apnoeic episodes, caffeine has become the standard of care in most developed countries, simply because it can be administered orally, has a longer half-life and a broader therapeutic range and is associated with a lower incidence of serious complications when compared with its counterparts.

Moreover, monitoring of serum concentrations as required for theophylline is not needed when caffeine is given, making its use easier and more practical for the NICU setting. However, it is worth noting that administration of methylxanthines such as caffeine may lead to short-term complications such as irritability, feed intolerance, gastric irritation and tachycardia (Henderson-Smart 2010). Other stimulants such as doxapram and ampakines have been tested recently but have not yet been adopted into standard practice (Morton 2016).

Description of the intervention

Whether non-prone body positions can compromise the physiological stability of spontaneously breathing preterm infants with recurrent apnoea is an important clinical question for NICU caregivers. Thus, the authors of this review set out to review all available evidence on effects of non-prone versus prone body positions on the incidence of AOP. Preterm infants are usually cared for in the supine, prone, left lateral or right lateral position, with limited changes in position, to reduce stress and allow them to sleep between nursing care procedures. However, prolonged positioning of the infant in any of these positions increases the risk of pressure ulcers, and repositioning of infants every two to four hours is encouraged (van der Burg 2016).

Although several studies have reported that prone positioning rather than supine positioning improves oxygenation and lung

function by optimising breathing strategy, researchers have argued more recently that oxygenation is not affected by positioning but instead follows an anatomical rather than a gravitational pattern (Gouna 2013). Moreover, studies on the effect of lateral positioning on oxygenation show conflicting results, with some reporting improvement and others describing no change in oxygenation (Brunherotti 2014; Gouna 2013; van der Burg 2016).

How the intervention might work

It has been suggested that prone positioning improves thoraco-abdominal synchrony and can stabilise the chest wall without affecting an infant's breathing pattern or oxygen saturation. Several studies have reported that prone positioning reduces AOP (Zhao 2011; Finer 2006), but for reducing the incidence of hypoxaemia and bradycardia among preterm infants, proponents of both prone and supine positions can be found (Heimann 2010; Bauschatz 2008). Additionally, researchers have found that tilting the head of a preterm infant in prone position at a 15- to 45-degree angle increases end-expiratory lung volume, improves oxygenation and decreases respiratory and heart rates (Jenni 1997; Dellagrammaticas 1991; Thoresen 1988), possibly as the result of decreased diaphragmatic fatigue, improved ventilation in lower segments of the lungs and enhanced ventilation/perfusion matching (Dellagrammaticas 1991; Thoresen 1988).

Why it is important to do this review

Body positioning is a non-invasive procedure that, when skilfully implemented, can provide comfort and containment while facilitating the interaction between infant and parents (Candia 2014; Peng 2014). If it is found that body positioning can reduce clinically significant apnoea in the preterm infant, use of more invasive measures to alleviate apnoea may be reduced or avoided altogether, leading to optimal management of apnoea in preterm infants.

A Cochrane review comparing effects of different body positioning on 581 hospitalised infants and children with acute respiratory distress syndrome (ARDS) found that the prone position was significantly superior to the supine position in terms of enhancing oxygenation. However, most participants in this study were ventilated preterm infants (i.e. not spontaneously breathing), leading review authors to conclude that the benefits of prone positioning may be most relevant to this specific subgroup of preterm infants (Gillies 2012). Likewise, a Cochrane review addressing effects of body positioning in 285 newborns receiving mechanical ventilation reported that the prone position slightly improved oxygenation in neonates undergoing mechanical ventilation but found no evidence of sustained improvement in clinically relevant outcomes (Balaguer 2013).

Thus, to further inform NICU caregivers and to contribute to the quality of current neonatal clinical care practices, authors of the current review sought to update included evidence to ascertain whether use of any specific body position over another results in benefit or harm for spontaneously breathing preterm infants with apnoea. This review is an update of a previous systematic review that assessed effects of positioning on cardiorespiratory functions of spontaneously breathing preterm infants with apnoea (Bredemeyer 2012).

OBJECTIVES

To determine effects of body positioning on cardiorespiratory parameters in spontaneously breathing preterm infants with clinically significant apnoea.

Subgroup analyses examined effects of body positioning of spontaneously breathing preterm infants with apnoea from the following subgroups.

- Gestational age < 28 weeks or birth weight less than 1000 grams.
- Apnoea managed with methylxanthines.
- Frequent apnoea (> 10 events/d).
- Type of apnoea measured (central vs mixed vs obstructive).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled clinical trials, including cross-over designs.

Types of participants

- Spontaneously breathing (i.e. receiving no respiratory support other than supplemental oxygen when needed) preterm infants (gestational age < 37 weeks) with apnoea of prematurity
- Infants receiving methylxanthines and those not receiving methylxanthines

Types of interventions

We sought to compare the following positions.

- Supine versus prone (lying on back vs lying on front).
- Supine versus right lateral (lying on back vs lying on right side).
- Supine versus left lateral (lying on back vs lying on left side).
- Prone versus right lateral (lying on front vs lying on right side).
- Prone versus left lateral (lying on front vs lying on left side).
- Right versus left lateral (lying on right side vs lying on left side).

We planned to analyse horizontal (flat) versus head-elevated positions separately for all body positions, when possible, as follows.

- Prone horizontal versus prone head elevated.
- Supine horizontal versus supine head elevated.
- Right lateral horizontal versus right lateral head elevated.
- Left lateral horizontal versus left lateral head elevated.

Types of outcome measures

Primary outcomes

- Episodes of apnoea - defined as cessation of breathing for longer than 20 seconds, or a shorter pause but associated with bradycardia or cyanosis (AAP 2003)
- Episodes of bradycardia - defined as a fall in heart rate to greater than 30% below baseline, or to less than 100 beats per minute, for 10 seconds or longer
- Episodes of oxygen desaturation - defined as a spontaneous fall in SpO_2 to ≤ 85% for 10 seconds or longer

Secondary outcomes

- Episodes of mixed events (or severe apnoea) - defined as cessation of breathing and a fall in heart rate to greater than 30% below baseline, or to less than 100 beats per minute, for 10 seconds or longer and a concurrent fall in SpO_2 to ≤ 85%
- Episodes of severe bradycardia with desaturation - defined as a fall in heart rate to greater than 30% below baseline, or to less than 100 beats per minute, for 10 seconds or longer and a concurrent fall in SpO_2 to ≤ 85%
- Need for assisted ventilation (intermittent positive-pressure ventilation (IPPV) or continuous positive airway pressure (CPAP))
- Duration of assisted ventilation, if any (IPPV or CPAP) (in days)
- Need for commencement of methylxanthines (caffeine, theophylline, etc.)
- Duration of use of methylxanthines, if any (in days)
- Complications associated with body positioning (e.g. skin breakdown, ulcers)
- Parental stress associated with type of body positioning assessed on a validated scale (e.g. Parental Stressor Scale: Neonatal Intensive Care Unit) during the intervention and over the remainder of the hospital stay
- Length of stay in hospital (in days)
- Short-term motor development up to 12 months' corrected age, as measured on a validated assessment tool
- Long-term motor development up to two years' corrected age, as measured on a validated assessment tool
- Neurodevelopment assessed at two years' corrected age, as measured on a validated assessment tool

Search methods for identification of studies

Electronic searches

We conducted the updated search in November 2016 and limited the search to the year 2011 and beyond, in an effort to retrieve all new studies published after the date of the search performed for the original review (March 2011).

We used criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) in the Cochrane Library; MEDLINE via PubMed (1966 to 14 November 2016); Embase (1980 to 14 November 2016); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 14 November 2016) and used the following search terms: ((apnoea OR apnea OR bradycardia) AND (body position OR position OR supine OR prone OR lateral OR side-lying OR upright OR tilting)), plus database-specific limiters for randomised controlled trials (RCTs) and neonates (see Appendix 1 for the full search strategies for each database). We applied no language restrictions.

We searched clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; the World Health Organization International Trials Registry and Platform www.whoint/ictrp/search/en/; the ISRCTN Registry).

Searching other resources

We examined the reference lists of all studies identified as eligible and other relevant systematic reviews to check for any studies not captured by our search. We also searched the abstracts of annual meetings of the Pediatric Academic Societies (1993 through 2014), the European Society for Pediatric Research (1995 through 2015), the UK Royal College of Paediatrics and Child Health (2000 through 2015) and the Perinatal Society of Australia and New Zealand (2000 through 2015). The 2015 abstracts of the Pediatric Academic Societies and the 2016 abstracts of the European Society for Pediatric Research, the UK Royal College of Paediatrics and Child Health, and the Perinatal Society of Australia and New Zealand were not yet available online at the date of our updated search.

Data collection and analysis

We used standard Cochrane systematic review methods, as documented in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors independently screened for eligibility the titles and abstracts of the studies retrieved by our search strategy. We retrieved for further assessment the full texts of articles judged as potentially eligible by at least one review author. Then, we independently screened, in duplicates, the full-text articles to assess for their eligibility; in cases of lack of consensus, the two review authors consulted an expert third review author.

Data extraction and management

We used the data extraction form available within Review Manager software (Review Manager 2014) to extract data on participants, interventions and control(s) and on outcomes of each included trial. One review author (RB) expanded and re-assessed the data previously extracted from each study, with blinding of the previously extracted data but no blinding for the authorship or journal publication of the studies. He resolved any discrepancy between his extracted data and that of the previous versions by consulting the review author involved in the earlier versions of the review (JF). When data were missing, unclear or incomplete, we made reasonable attempts to contact trial authors to obtain the required information. When more than one report was published for the same study, we selected the report presenting the most data as the primary reference for the review. One review author then entered data into Review Manager software (Review Manager 2014), and a second review author verified the data.

Extracted data included the following.

- Participant characteristics.
- Inclusion and exclusion criteria.
- Numbers of enrolled participants and attrition rates (when possible).
- Details of interventions.
- Outcomes measured.
- Duration of study and frequency of measurements.

Assessment of risk of bias in included studies

Review authors independently assessed risk of bias for the included studies using the criteria outlined in the *Cochrane Handbook for*

Systematic Reviews of Interventions (Higgins 2011). We resolved disagreements successfully by discussion and therefore found it unnecessary to involve a review arbiter. We completed the 'Risk of bias' table by appraising the following methodological issues.

- Selection bias: random sequence generation and selection bias, i.e.:
  - random sequence generation (biased allocation to interventions) due to inadequate generation of a randomised sequence; and
  - allocation concealment: selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment.
- Blinding of participants and personnel: performance bias due to knowledge of allocated interventions by participants and personnel during the study.
- Blinding of outcome assessment: detection bias due to knowledge of allocated interventions by outcome assessors.
- Incomplete outcome data: attrition bias due to quantity, nature or handling of incomplete outcome data.
- Selective reporting: reporting bias due to selective outcome reporting.
- Other bias: bias due to problems not covered elsewhere in the table.

See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

As planned a priori, we analysed continuous variables by using weighted mean differences and 95% confidence intervals (CIs). All outcome data for the included trials were continuous. None of the outcomes of interest were categorical variables, although we prespecified that we would analyse such variables, if encountered, by using risk ratios (RRs) and risk differences (RDs) with 95% CIs. We used Review Manager software in conducting the meta-analyses (Review Manager 2014).

Unit of analysis issues

Cross-over trials

We analysed cross-over trials by following the recommendations provided in Elbourne 2002, which state that use of the cross-over design should be restricted to situations in which it is unlikely to have carry-over of treatment effect across periods. We included all eligible cross-over trials in the meta-analysis, but we assessed and discussed the likelihood of a carry-over effect from one intervention to another (i.e. different body positions).

See Risk of bias in included studies and Other potential sources of bias for further discussion.

Assessment of heterogeneity

We assessed heterogeneity between included trials, using the formal and commonly applied statistic to assess heterogeneity - the I^2 statistic. This test describes the percentage of total variation observed across studies due to heterogeneity rather than to sampling (random) error (Higgins 2011). We graded the degree of heterogeneity as 0% to 25% for no heterogeneity, 25% to 49% for low degree of heterogeneity, 50% to 74% for moderate degree of heterogeneity and 75% to 100% for high degree of heterogeneity.

When we found evidence of apparent or statistical heterogeneity, we attempted to assess the source of the heterogeneity by performing sensitivity and subgroup analyses to discern sources of bias or methodological differences between heterogeneous trials.

Assessment of reporting biases

We did not examine funnel plots to identify potential publication bias because we found an insufficient number of trials on the topic.

Data synthesis

We carried out statistical analyses by using RevMan 5.3 (Review Manager 2014). Ideally, we would have used first-period data from cross-over trials and combined them with data obtained from parallel studies according to the recommendations of Elbourne 2002: "the results of two or more cross-over trials might be combined, but with this pooled result kept separate from the data from parallel group trials". Unfortunately, we were not able to obtain first period data for any of the included cross-over studies and we found no eligible trials of parallel design.

Therefore, we meta-analysed only the findings of trials using a cross-over design. We used fixed-effect inverse variance meta-analyses when combining data from trials examining the same intervention and using similar trial populations and methods. If we deemed similarity of populations, interventions and/or methods to be insufficient, we did not perform a meta-analysis.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: episodes of apnoea, episodes of severe apnoea (i.e. mixed events), episodes of oxygen desaturation, episodes of bradycardia and episodes of severe bradycardia.

Two review authors independently assessed the quality of evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (and two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates and presence of publication bias. We used the GRADEpro 2008 Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in assignment of the quality of a body of evidence to one of four grades.

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses when possible.

- Extremely preterm infants (gestational age < 28 weeks).
- Preterm infants with low birth weight (< 1000 grams).
- Preterm infants with different postnatal gestational age (< 28 weeks vs ≥ 28 weeks).
- Preterm infants with apnoea managed with methylxanthines.
- Preterm infants with frequent apnoea (> 10 events per day).
- Preterm infants with different types of apnoea (central vs mixed vs obstructive).

However, we did not perform subgroup analyses because available data for the specified subgroups were insufficient.

RESULTS

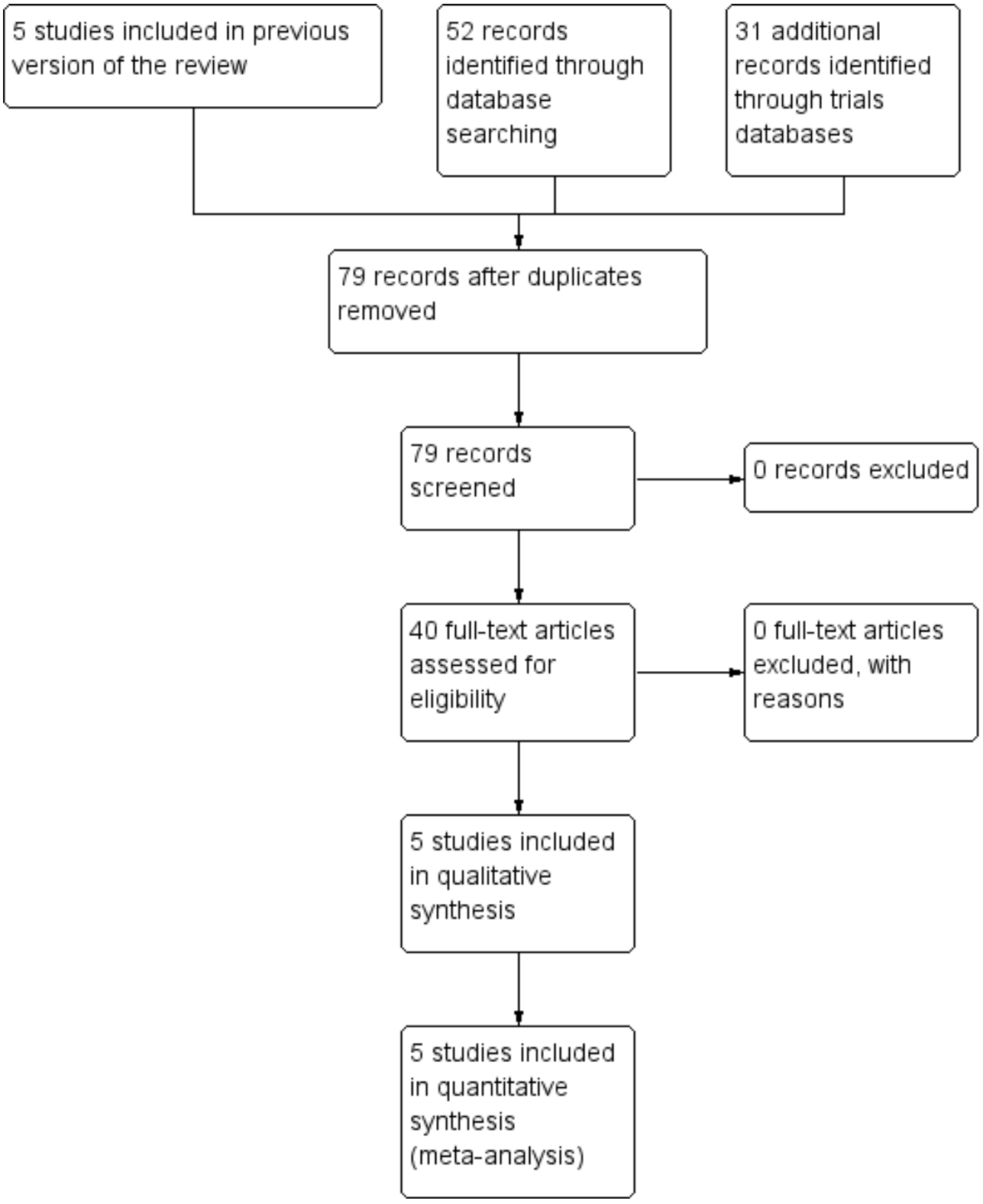
Description of studies

See the Characteristics of included studies table and the Characteristics of excluded studies table.

Results of the search

By using the search strategy of the original review, we identified five small eligible randomised controlled clinical trials of cross-over design (N = 114) that examined body positioning for spontaneously breathing preterm infants with apnoea (Bredemeyer 1992 (N = 21); Bredemeyer 2004 (N = 45); Heimler 1992 (N = 14); Jenni 1997 (N = 12); Keene 2000 (N = 22)). For the review update, we identified 34 records through a database search (2011-2016). We performed other searches and identified six additional records from other sources. After duplicates were removed, we had 40 records. We reviewed the abstract or full text of identified articles and found no new relevant studies (Figure 1).

Figure 1. Study flow diagram: review update.



We also found one study awaiting classification (Yaming 2015).

Included studies

Population

All infants enrolled in these trials were spontaneously breathing preterm infants at less than 37 weeks' gestational age. Bredemeyer 1992 studied infants at < 34 weeks' gestation (mean gestation 28.3 weeks), Bredemeyer 2004 studied infants at < 33 weeks (median gestational age 27 weeks), Heimler 1992 studied infants at < 37 weeks (range 26 to 36 weeks, mean 29.7 weeks), Jenni 1997 studied infants at < 32 weeks (range 26 to 31 weeks, mean 28 weeks) and Keene 2000 studied infants at < 34 weeks (range 24 to 30 weeks, mean 26.9 weeks). Investigators reported a wide range of postnatal ages of infants at the time of enrolment in each trial (range three to 77 days). One trial (Keene 2000) reported time of enrolment as postconceptual age (range 28 to 36 weeks) rather than postnatal age, as was reported in the other trials.

Interventions

All included studies were randomised controlled clinical trials of cross-over design involving alternating periods in different body positions. Heimler 1992 reported a two-period cross-over trial, with each body position (supine or prone) studied over a 12-hour period for two consecutive nights. Jenni 1997 described a multiple cross-over trial in which body position (prone horizontal or prone elevated) was changed every six hours for 48 hours. Keene 2000 conducted a multiple cross-over trial in which body position (supine or prone) was changed every six hours for 24 hours. Bredemeyer 1992 performed a multiple cross-over trial with body position (prone one, prone two, left lateral or right lateral) changed every three hours for 48 hours. Bredemeyer 2004 used a multiple cross-over design in a trial in which body position (prone horizontal, prone elevated, right lateral one and two, left lateral one and two) was changed every four hours for 24 hours.

For further details, see Other potential sources of bias.

Major outcomes assessed

Four trials (Bredemeyer 1992; Bredemeyer 2004; Heimler 1992; Keene 2000) reported outcomes for episodes of apnoea.

Bredemeyer 1992 and Bredemeyer 2004 defined apnoea as cessation of breathing for longer than 20 seconds or cessation of breathing for less than 20 seconds if associated with a fall in heart rate to greater than 30% below baseline. Investigators determined frequency by counting the number of apnoeic events that occurred throughout the time the infant spent in each body position. Keene 2000 defined apnoea as cessation of breathing for 10 seconds or longer and classified its severity as mild (lasting < 15 seconds) or clinically significant (lasting ≥ 15 seconds). We used only the clinically significant definition of apnoea (i.e. ≥ 15 seconds) in our meta-analysis. In contrast, Heimler 1992 defined apnoea as cessation of breathing for six seconds or longer and classified its severity as mild (lasting < 11 seconds), moderate (lasting 11 to 15 seconds) or severe (lasting ≥ 15 seconds). We used only the latter definition of apnoea in our meta-analysis. We chose definitions that were closely aligned with our primary outcomes as defined a priori.

Bredemeyer 2004 was the only study that reported outcomes for severe apnoea (i.e. mixed events), which was defined as cessation of breathing and a fall in heart rate to greater than 30% below baseline and a concurrent fall in oxygen saturation to less than 85%.

Studies addressing bradycardia used different definitions for this term. Bredemeyer 2004 defined severe bradycardia as a fall in heart rate to greater than 30% below baseline associated with a significant fall in oxygen saturation greater than 10% and an alteration in respiratory pattern suggesting decreased respiratory efforts. Heimler 1992 defined bradycardia as a fall in heart rate to less than 100 beats per minute lasting five seconds or longer. Jenni 1997 defined bradycardia as a fall in heart rate to less than 90 beats per minute. Keene 2000 defined bradycardia as a fall in heart rate to less than 100 beats per minute, classified as mild (drop to reach 90 to 99 beats per minute) or clinically significant (drop to < 90 beats per minute). We used data from the latter definition in our meta-analysis. All studies determined bradycardia by counting the number of bradycardia events that occurred in each body position.

Two studies (Bredemeyer 2004; Jenni 1997) measured severe bradycardia but used slightly different definitions; Bredemeyer 2004 defined severe bradycardia as a fall in heart rate to greater than 30% below baseline for 10 seconds or longer and a concurrent fall in oxygen saturation to less than 85%. Jenni 1997 defined severe bradycardia as a fall in heart rate to less than 90 beats per minute and a concurrent decrease in oxygen saturation to less than 80%.

Moreover, three of the studies included in the review measured 'episodes of oxygen desaturation'. Bredemeyer 2004 defined oxygen desaturation as the number of episodes during which oxygen saturation fell to less than 85% for longer than 10 seconds without occurrence of an apnoea or bradycardia event. Keene 2000 defined oxygen desaturation as the number of episodes during which oxygen saturation fell to less than 90% and classified its severity as mild (drop to reach 80% to 90%) or clinically significant (drop to less than 80%). For our meta-analysis, we used data reported for the drop in oxygen saturation to less than 80% for the latter trial. Finally, Jenni 1997 defined oxygen desaturation as the number of episodes during which oxygen saturation fell to less than 80%.

Excluded studies

We excluded seven studies (Bhat 2003; Dellagrammaticas 1991; Heimann 2010; Kurlak 1994; Nimavat 2006; Pichler 2001; Reher 2008). See the Characteristics of excluded studies table.

Risk of bias in included studies

We have provided details of methodological quality assessments in the Characteristics of included studies table. We completed a 'Risk of bias' table for each eligible study and have presented our overall assessment of risk of bias in a 'Risk of bias' graph (Figure 2) and a 'Risk of bias' summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

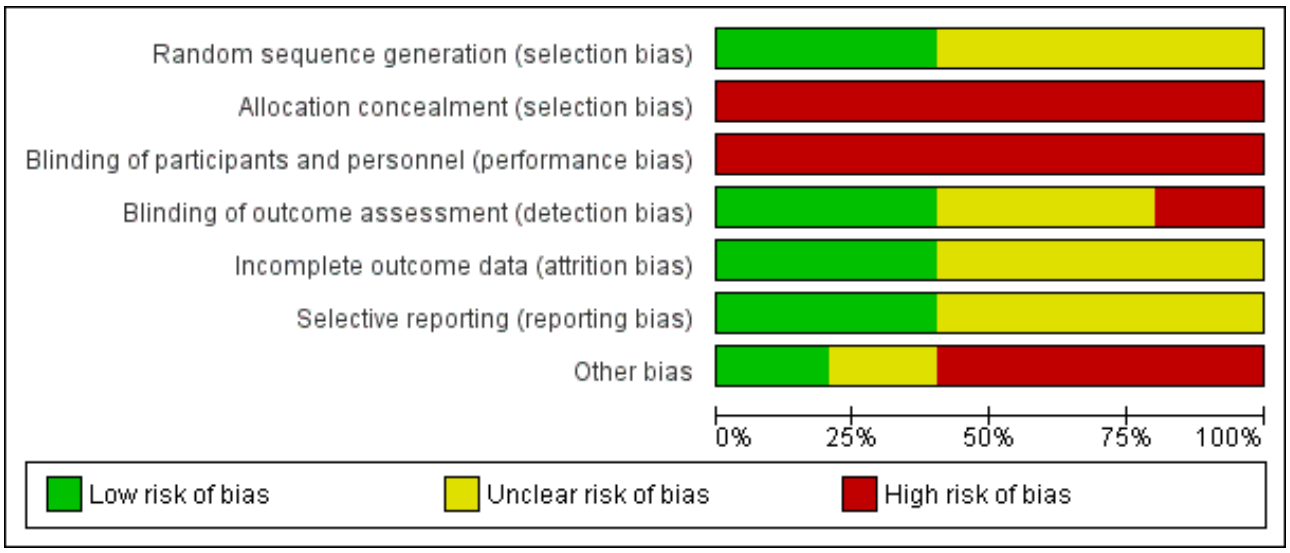
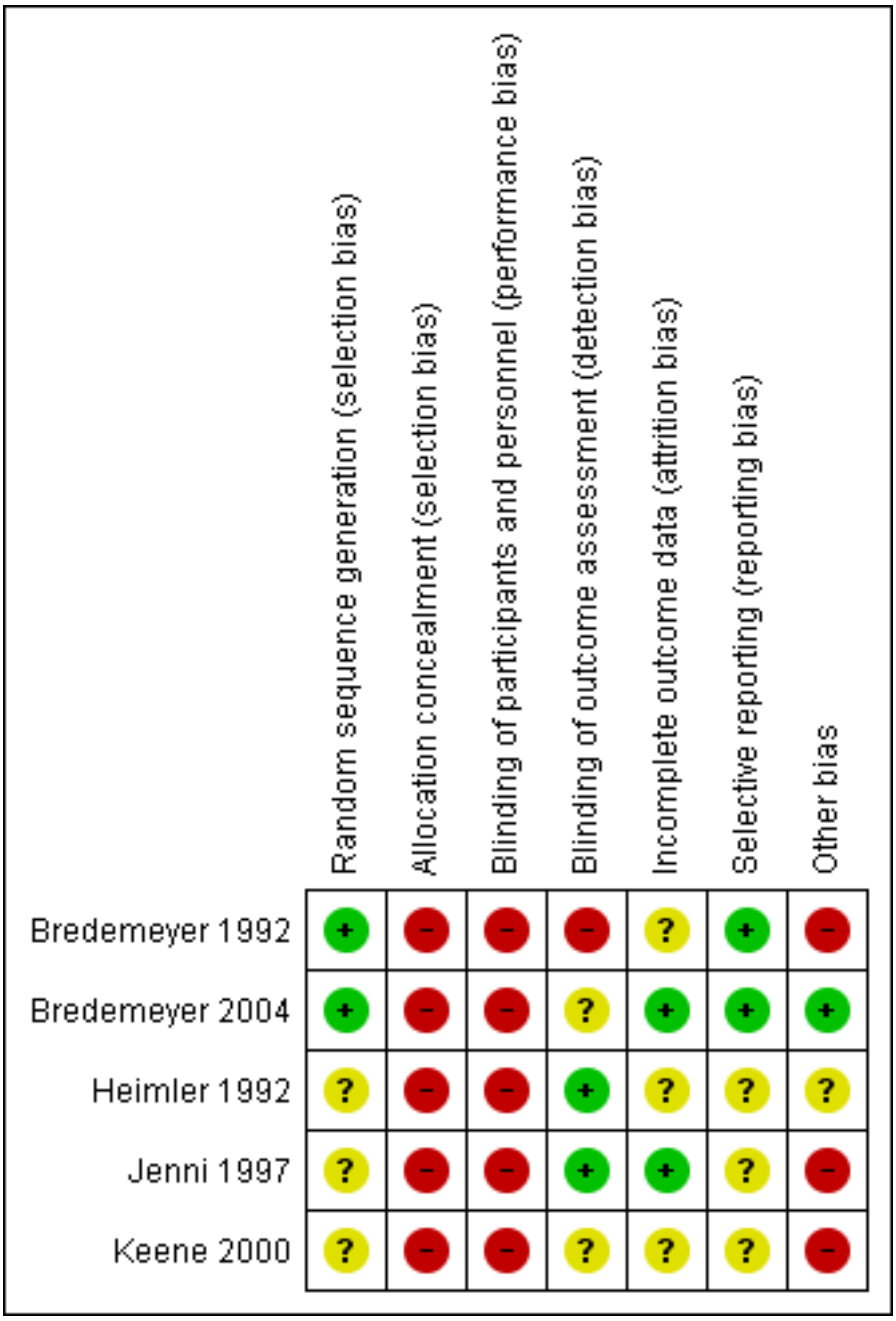


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Of the five included studies, Bredemeyer 1992, Bredemeyer 2004 and Heimler 1992 reported adequate sequence generation in that all used a quasi-randomisation method to randomly assign infants to specific body positions. Bredemeyer 1992 and Bredemeyer 2004 used a Latin square to randomise infants, and Heimler 1992 used sealed envelopes for randomisation (although it was unclear if envelopes were opaque and sequentially numbered for true non-quasi randomisation).

Randomisation within Jenni 1997 and Keene 2000 was unclear because investigators provided no data on how randomisation was performed.

All included studies had high risk of bias for allocation concealment because randomisation of each infant could be figured out by anyone who knew the position in which an infant was currently placed.

Blinding

All included studies had high risk of performance bias regarding blinding of participants and personnel. Regarding blinding of outcome assessors (detection bias), only Bredemeyer 1992 had high risk of bias; Heimler 1992 and Jenni 1997 had low risk of bias; and Bredemeyer 2004 and Keene 2000 had unclear risk of bias. As for blinding of data analysts (also detection bias), Bredemeyer 2004, Heimler 1992 and Jenni 1997 had low risk of bias because

blinding was adequate at the analysis stage through different methods; we judged Keene 2000 and Bredemeyer 1992 to have unclear risk of bias owing to lack of data regarding blinding at the data analysis stage.

Incomplete outcome data

Risk of attrition bias (i.e. missing data) was low in Bredemeyer 2004 and Jenni 1997, which reported data for all enrolled participants or provided adequate justification for cases in which data were missing (e.g. Bredemeyer 2004). Risk of attrition bias was unclear in Bredemeyer 1992, Heimler 1992 and Keene 2000.

Selective reporting

Risk of reporting bias was low in Bredemeyer 1992 and Bredemeyer 2004, as both studies reported the outcomes prespecified in their corresponding trial protocols. Remaining studies had unclear risk of reporting bias; we were unable to obtain study protocols to compare primary outcomes defined a priori versus those actually reported.

Other potential sources of bias

Inclusion of a wash-out period is important in cross-over trials, in which a carry-over effect may occur from one treatment period to the next.

Risk of bias was high for a carry-over effect in Bredemeyer 1992, Jenni 1997 and Keene 2000, as investigators reported no adequate wash-out intervals between different interventions (body positions). In fact, changes from one intervention (body position) to another were almost immediate. On the other hand, risk of a carry-over treatment effect was low in Bredemeyer 2004 and Heimler 1992.

Heimler 1992 reported a 12-hour wash-out period between changes in body position, thus decreasing the possibility of a carry-over effect from one intervention body position to another. Bredemeyer 2004 introduced an additional seventh position at the end of each sequence to show that the sequence of body positions makes no difference with regards to the outcomes of interest, and thus no carry-over treatment effect occurred. Moreover, in Heimler 1992, even though infants were assigned to the supine position, they were nursed prone for one hour after each feed to 'prevent aspiration'. This may have influenced the outcome measure of apnoea during this period because both the supine group and the prone group were in the prone position one hour post feed.

Effects of interventions

See: **Summary of findings for the main comparison** Supine versus prone positioning; **Summary of findings 2** Prone horizontal versus right lateral horizontal positioning; **Summary of findings 3** Prone horizontal versus left lateral horizontal positioning; **Summary of findings 4** Right lateral versus left lateral positioning; **Summary of findings 5** Prone horizontal versus prone head elevated positioning; **Summary of findings 6** Right lateral horizontal versus right lateral elevated positioning; **Summary of findings 7** Left lateral horizontal versus left lateral elevated positioning

Supine versus prone (Comparison 1)

Meta-analysis (Heimler 1992; Keene 2000; 36 infants) revealed no significant difference for apnoea (mean difference (MD) 1.09, 95% confidence interval (CI) 0.65 to 2.82). The Chi^2 test showed moderate heterogeneity (I^2 = 61%), but results were not statistically significant (P = 0.11). However, heterogeneity could be due to the different gestational ages of infants included in the two studies. One study (Keene 2000) found no significant difference for oxygen desaturation (MD 0.80, 95% CI 3.19 to 4.79), and meta-analysis (Heimler 1992; Keene 2000; 36 infants) revealed no significant difference for bradycardia (MD -0.13, 95% CI -3.20 to 2.94). We did not assess severe bradycardia or severe apnoea.

Prone versus right lateral (Comparison 2)

Meta-analysis (Bredemeyer 1992; Bredemeyer 2004; 65 infants) revealed no significant difference for apnoea (MD 0.48, 95% CI -0.19 to 1.15). One study (Bredemeyer 2004) showed no significant difference for oxygen desaturation (MD -1.86, 95% CI -4.29 to 0.56), severe apnoea (MD 0.05, 95% CI -0.45 to 0.54), bradycardia (MD -0.59, 95% CI -2.41 to 1.23) or severe bradycardia (MD -0.32, 95% CI -1.02 to 0.39).

Prone versus left lateral (Comparison 3)

Meta-analysis (Bredemeyer 1992; Bredemeyer 2004; 66 infants) revealed no significant difference for apnoea (MD 0.20, 95% CI -0.75 to 1.15). One study (Bredemeyer 2004) showed no significant difference for oxygen desaturation (MD -1.44, 95% CI -3.81 to 0.92), severe apnoea (MD 0.11, 95% CI -0.38 to 0.60), bradycardia (MD -0.17, 95% CI -0.94 to 0.60) or severe bradycardia (MD -0.22, 95% CI 0.94 to 0.49).

Right lateral versus left lateral (Comparison 4)

Meta-analysis (Bredemeyer 1992; Bredemeyer 2004; 66 infants) revealed no significant difference for apnoea (MD -0.27, 95% CI -1.10 to 0.57). One study (Bredemeyer 2004; 45 infants) showed no significant difference for oxygen desaturation (MD 0.42, 95% CI -2.42 to 3.26), severe apnoea (MD 0.01, 95% CI -0.40 to 0.42), bradycardia (MD 0.42, 95% CI -1.43 to 2.27) or severe bradycardia (MD 0.09, 95% CI -0.68 to 0.87).

Prone horizontal versus prone head elevated (Comparison 5)

Meta-analysis (Bredemeyer 1992; Bredemeyer 2004; 65 infants) revealed no significant difference for apnoea (MD -0.18, 95% CI -1.09 to 0.73) and no significant difference for oxygen desaturation (Jenni 1997; Bredemeyer 2004; 56 infants) (MD -0.62, 95% CI -2.81 to 1.56). The Chi^2 test showed moderate heterogeneity (I^2 = 68%), but results were not statistically significant (P = 0.08). One study (Bredemeyer 2004) found no significant difference for severe apnoea (MD -0.24, 95% CI -0.83 to 0.35). Meta-analysis of two studies (Jenni 1997; Bredemeyer 2004; 56 infants) revealed no significant difference for bradycardia (MD -0.14, 95% CI -1.03 to 0.74) and no significant difference for severe bradycardia (MD -0.28, 95% CI -1.15 to 0.59).

Right lateral horizontal versus right lateral head elevated (Comparison 6)

One study (Bredemeyer 2004) found no significant difference for apnoea (MD -0.79, 95% CI -2.26 to 0.69), oxygen desaturation (MD 0.03, 95% CI -3.06 to 3.11), severe apnoea (MD -0.14, 95% CI -0.69 to 0.41), bradycardia (MD 0.34, 95% CI 1.54 to 2.22) or severe bradycardia (MD 0.60, 95% CI -0.25 to 1.46).

Left lateral horizontal versus left lateral head elevated (Comparison 7)

One study (Bredemeyer 2004) found no significant difference for apnoea (MD 0.46, 95% CI -0.34 to 1.26), oxygen desaturation (MD 0.63, 95% CI -2.09 to 3.35), severe apnoea (MD 0.18, 95% CI -0.18 to 0.54), bradycardia (MD 0.08, 95% CI -0.71 to 0.88) or severe bradycardia (MD -0.17, 95% CI -0.93 to 0.58).

However, no studies compared supine versus right lateral, supine versus left lateral and/or supine horizontal versus supine head elevated.

Morover, none of the included studies assessed the primary outcome of oxygenation nor the secondary outcomes of type of apnoea measured in each body position (central, mixed or obstructive), addition of assisted ventilation (IPPV and CPAP), addition of methylxanthines, complications associated with body position (e.g. skin breakdown, ulcers), parental satisfaction with type of body position, duration of assisted ventilation (IPPV and CPAP) (in days), duration of use of methylxanthines (in days) and length of stay in hospital (in days).

DISCUSSION

Review authors identified a total of 12 studies and excluded seven from the review (Bhat 2003; Dellagrammaticas 1991; Heimann 2010; Kurlak 1994; Nimavat 2006; Pichler 2001; Reher 2008). We included five studies (Bredemeyer 1992; Bredemeyer 2004; Heimler 1992; Jenni 1997; Keene 2000) (N = 114) in this review and in its meta-analyses.

Overall, none of the individual studies nor meta-analyses showed differences in cardiorespiratory outcomes in comparisons of different preterm infant body positions (supine vs prone; prone vs right lateral; prone vs left lateral; right lateral vs left lateral; prone horizontal vs prone head elevated; right lateral horizontal vs right lateral head elevated; left lateral horizontal vs left lateral head elevated).

All five included studies had small sample sizes, and most meta-analyses included only one or two studies. We found no studies investigating supine versus right lateral, supine versus left lateral or supine horizontal versus supine head elevated. No included studies addressed any of the secondary outcomes.

Summary of main results

Overall, we found insufficient evidence to determine effects of body positioning on apnoea, bradycardia and oxygen saturation in spontaneously breathing preterm infants with clinically significant apnoea.

Overall completeness and applicability of evidence

The largest analysis included only 66 infants and did not reveal a moderate effect of body positioning on any measured outcomes.

Quality of the evidence

Overall, we found evidence of low to very low quality for all of the major outcomes of this review. The factors that most affected the quality of evidence were high or unclear risk of allocation concealment and imprecision (broad confidence interval), high or unclear risk of performance bias, high or unclear risk of detection bias and reliance upon a single study (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7). In addition, use of a cross-over design prevented measurement of effects on late outcomes (e.g. long-term neurodevelopment). Moreover, the order in which treatments were administered may have affected the outcome, except in the case of Bredemeyer 2004, in which investigators introduced an additional period to account for this. Furthermore, a "carry-over" effect from one position to another may have occurred because of the absence of an adequate "wash-out" period between treatments in all but two included studies (Bredemeyer 2004; Heimler 1992). See also Risk of bias in included studies.

Potential biases in the review process

We were not able to obtain first-period data from the authors of any of the cross-over trials included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

We concluded that evidence is insufficient to show effects of body positioning on apnoea, bradycardia and oxygen saturation in spontaneously breathing preterm infants with clinically significant apnoea. Although the prone position seems to benefit ventilated preterm infants (Balaguer 2013; Gillies 2012), the same cannot be said about the prone position in spontaneously breathing (i.e. non-ventilated) preterm infants. In addition, as a result of the association of the prone position with sudden infant death syndrome (SIDS) (AAP 2003; Blair 2006), all hospitalised infants placed in the prone position must undergo continuous monitoring of cardiorespiratory and peripheral capillary oxygen saturation (SpO_2).

None of the trials included in our review reported complications or adverse effects related to the use of supine, prone or lateral body positions. This presents limitations in making conclusions and potential recommendations for clinical practice. Moreover, in all of the included studies, researchers placed infants in each body position only for a short duration (three to 12 hours). Therefore, they were unable to assess any long-term effects associated with prolonged placement of an infant in any of these positions, such as flattened posture, high extensor tone or altered head shape.

Implications for research

The fact that no new studies have been conducted in the past four years on this topic may indicate that body positioning could have little or no effect on cardiorespiratory parameters of spontaneously breathing preterm infants. However, this statement remains to be tested by future evidence. Evidence is insufficient to show effects of body positioning on cardiorespiratory parameters of preterm infants. The benefit or harm of one body position over another cannot be ensured because trials have been few, have included only a small number of participants and have exhibited weakness in their corresponding designs.

Therefore, large, international, multi-centre, randomised controlled clinical trials are needed to better assess effects of positioning on cardiorespiratory parameters of spontaneously breathing preterm infants with recurrent apnoea. Researchers should also collect clinically meaningful data on mortality,

morbidity, recovery variables and adverse effects associated with allocated positions and should seek to determine the optimal frequency and timing of different positions for providing maximal sustained benefit for the infant's well-being and development. Further research into the effectiveness of other body positions may also be needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bredemeyer 1992

Methods	Quasi-randomised controlled cross-over trial
Participants	Participants: 21 preterm infants with 3 or more episodes of clinical apnoea not associated with feeds and with no other conditions (otherwise healthy) who were not receiving assisted ventilation including nasal CPAP Infants treated with theophylline had to show stability for at least 48 hours before study entry. 7 infants were receiving supplemental ambient oxygen and were nursed in convenient isolettes. Mean birth weight: 1220 grams Mean gestational age: 28.3 weeks
Interventions	Lateral (experimental) vs prone (control) position Body position was changed every 3 hours, with each infant spending 12 hours in each body position for a period of 48 hours, and with each infant acting as his/her own control. Instrument(s) of measurement included: • a 3-channel cardiorespiratory impedance monitor, used to record respiration pattern (channel 1), oxygen saturation (channel 2) and heart rate (channel 3); and • a pulse oximetry polygraph, used to record apnoeic events.
Outcomes	Episodes of apnoea were defined as: • cessation of breathing for ≥ 20 seconds; and • cessation of breathing for < 20 seconds but associated with a simultaneous fall in heart rate to > 30% below baseline. Frequency of apnoea was measured as the number of apnoeic events that occurred for each body position.

Bredemeyer 1992 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were allocated to their specific positions by a Latin square randomisation design after they were randomly assigned a sequence.
Allocation concealment (selection bias)	High risk	"Prior to commencement of the study each subject was 'randomly assigned' to a sequence 1, 2, 3 or 4, and the prone and lateral positions were allocated using a Latin Square". However, infants were shifted every 3 hours to the other position of the sequence defined in the Latin square; thus anyone who knew the previous position of the infant could easily know the infant's sequence number.
Blinding of participants and personnel (performance bias) All outcomes	High risk	High possibility of performance bias was due to knowledge of allocated interventions by personnel attending the infants. The statement "If the body position of the infant was changed during these time periods for routine medical or nursing interventions, the infant was returned to the 'appropriate position' of the sequence as soon as possible" indicates that personnel knew the sequence of all infants who had to receive some kind of medical or nursing intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	High possibility of detection bias was due to knowledge of allocated interventions by outcome assessors. However, no information was reported on whether blinding occurred at the data analysis stage.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was reported on missing outcome data or loss to follow-up and how these were handled. The paper does not mention or tabulate how many or if all enrolled infants (21) had data provided.
Selective reporting (reporting bias)	Low risk	The study was undertaken as per protocol, and all predefined outcomes of interest were reported in the final manuscript.
Other bias	High risk	Carry-over of treatment effect was noted. The order in which interventions were administered may have affected outcomes, especially because no "wash-out" period between interventions was reported.

Bredemeyer 2004

Methods	Quasi-randomised controlled cross-over trial
Participants	Participants: 36 clinically stable preterm infants (19 males and 17 females) with a history of recurrent apnoea sustaining at least 3 clinical events documented during the previous 24 hours but with no evidence of intercurrent illness known to be associated with apnoea (otherwise healthy), who were not receiving assisted ventilation including nasal CPAP Infants with a diagnosis of gastro-oesophageal reflux, with haemoglobin < 80 g/L or with development of grade 3/4 intraventricular haemorrhage were excluded from the study.

Bredemeyer 2004 *(Continued)*

	Before study initiation, all infants received intragastric feedings to at least 90 mL/kg/d. After initiation of the study: • 29 infants (81%) received feedings with breast milk exclusively; • 29 infants (81%) received caffeine therapy and had to show a stable regimen for at least 24 hours before entry into the study; and • 17 infants (47%) were receiving supplemental oxygen (92%-96% inspired oxygen). Only 1 infant developed grade 1/2 intraventricular haemorrhage. All infants were housed in incubators. Median gestational age at birth: 27 weeks (range 24-33 weeks) Median postnatal age at entry to the study: 22.5 days (range 3-77 days) Median birth weight: 1300 grams (range 800-1900 grams)
Interventions	Infants were initially allocated to 1 of 6 body positions - prone 1, prone 2, right lateral 1, right lateral 2, left lateral 1 and left lateral 2 - via assignment of a sequence number from 1 to 6, respectively, via a Latin square. Body position was changed every 4 hours over a period of 24 hours, with each infant acting as his/her own control and going through all 6 positions. When an infant was in any of the positions '1', he/she was placed in a horizontal or flat position. When the infant was rotated to any of the positions '2', he/she was placed in an elevated position on the mattress at a 15 degree elevation angle. An added seventh period of monitoring lasting for 4 hours at the end of each of the 6 sequences accounted for the remaining 4 hours of the 28-hour monitoring period. Infants went through this 4-hour period to reveal adverse effects that may have been associated with movement of the infant from the last position in the sequence to the next one in the sequence, just to show that the sequence of body positions makes no difference with regards to the outcomes of interest (Hypothesis 9). Instrument(s) of measurement included: • a neonatal cardiorespiratory monitor (Neo-Trak 502 Infant Monitor; Corometrics Medical Systems Inc., Wallingford, Connecticut, USA), used to record respiratory effort (apnoeic events) and heart rate (bradycardiac events); and • a pulse oximeter (Nellcor Symphony N-3000-U20; Nellcor Inc., Chula Vista, California, USA), used to measure oxygen saturation.
Outcomes	• Episodes of apnoea, defined as cessation of breathing lasting ≥ 20 seconds, or lasting < 20 seconds with a concomitant fall in heart rate to > 30% below baseline • Episodes of bradycardia, defined as a fall in heart rate to > 30% below baseline for ≥ 10 seconds • Episodes of oxygen desaturation, defined as the number of episodes during which oxygen saturation fell to < 85% for > 10 seconds (the total time (minutes) each infant spent with oxygen saturation < 85% in each body position was also documented) • Episodes of severe bradycardia, defined as a fall in heart rate to > 30% below baseline for ≥ 10 seconds and a concurrent fall in oxygen saturation to < 85% • Episodes of mixed events (apnoea with bradycardia and desaturation), defined as cessation of breathing for ≥ 20 seconds and a fall in heart rate to > 30% below baseline and a concurrent fall in oxygen saturation to < 85%
Notes	

Bredemeyer 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were allocated to specific positions by a Latin square randomisation design after they were randomly assigned a sequence.
Allocation concealment (selection bias)	High risk	"Prior to commencement of the study each subject was 'randomly assigned' to a sequence 1, 2, 3, 4, 5 or 6. The six body positions were allocated using a Latin Square". However, infants were shifted every 4 hours to the other position of the sequence defined in the Latin square; thus anyone who knew the previous position of the infant could easily know the infant's sequence number. "The randomization process was not blinded to the researcher, as it was imperative that all body positions were equally represented in the seven time zones of the study design".
Blinding of participants and personnel (performance bias) All outcomes	High risk	High possibility of performance bias was due to knowledge of allocated interventions by nurses attending the infants. The statement "Position change times and correct body position sequences for each infant was outlined on the nursing care plan so that the nurses could readily follow the study protocol" indicates that nurses attending the infants knew the sequence of all of these infants.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	High possibility of detection bias was due to knowledge of allocated interventions by outcome assessors (nurses). "The nurse caring for the infant also recorded the clinical events". However, low possibility of data analysis bias was noted in that "The respiratory, cardiac, and oxygen saturation waveforms could only be accessed by the investigator during the data analysis phase of the project. Both investigator and clinician were blinded to the 'download' of these data until the infant completed the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 45 infants who entered the study there were 9 infants whose data were incomplete due to 'computer downloads that were not correctly saved, and were unable to be recovered' by the investigator for analysis. Each of these 9 infants had one position (four hours) of lost data resulting in missing values sufficient to confound the multivariate analyses". "These 9 infants were removed to 'ensure consistency in the characteristics and number of subjects throughout all phases of the analyses". This left a cohort of 36 infants, who completed the study protocol with complete data sets provided for all.
Selective reporting (reporting bias)	Low risk	The study was undertaken as per protocol.
Other bias	Low risk	No carry-over of treatment effect was noted. The order in which interventions were administered may have affected the outcomes; this was accounted for by introducing a seventh 4-hour period position at the end of each sequence.

Heimler 1992

Methods	Randomised controlled cross-over trial

Heimler 1992 *(Continued)*

Participants	Participants: 14 preterm infants with recent clinical apnoea but with no other conditions (otherwise healthy) Infants did not receive supplemental oxygen or respiratory support at the time of the study. All infants were receiving enteral feeds - bolus feeding by nipple or intermittent gavage. Eight (57%) infants received maintenance methylxanthines (dosage not mentioned). Nine infants had previous RDS and were intubated up to 8 days before study initiation. Infants with bronchopulmonary dysplasia were excluded from the study. More mature infants were studied at an earlier age. Mean gestational age at birth: 29.7 ± 2.8 weeks (range 26-34 weeks) Postnatal age: 7-59.5 days Mean birth weight: 1381 ± 474 grams (range 840-2290 grams)
Interventions	Supine vs prone position. Each infant had two 12-hour consecutive nocturnal studies - 1 in the prone position and 1 in the supine position. Infants spent most of the study time in assigned positions. No attempt was made to keep the head in the midline position, and neck and shoulders were supported to prevent neck flexion. Breathing pattern, nasal airflow, respiratory effort, heart rate and oxygen saturation were studied by nocturnal 12-hour consecutive impedance cardiorespirography (pneumography) and were documented on a multi-channel recorder. Episodes of obstructive or mixed apnoea ≥ 6 seconds were counted manually by an investigator who was blinded to the body position in use. Episodes of generalised body movements that resulted in an abrupt fall in heart rate pattern on the oximeter, without coincident bradycardia, were excluded from the analysis.
Outcomes	• Episodes of apnoea, measured as the number of cessations of breathing per recording, with each lasting ≥ 6 seconds and classified by severity as: - Mild (6-11 seconds); - Moderate (11-15 seconds); or - Severe (≥ 15 seconds). • Episodes of bradycardia, defined as a fall in heart rate to less than 100 beats/min for ≥ 5 seconds • Episodes of oxygen desaturation, defined as a drop in oxygen saturation to < 87.5% for ≥ 10 seconds
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The order was assigned at random by sealed envelopes", but it is unclear if the envelopes were opaque and sequentially numbered.

Heimler 1992 *(Continued)*

Allocation concealment (selection bias)	High risk	Infants assigned to either position can be easily identified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	High possibility of performance bias was due to knowledge of allocated interventions by personnel attending the infants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low possibility of detection bias was due to blinding of allocated interventions by the outcome assessor. "Obstructive or mixed apnoea periods ≥ 6 seconds duration and oxygen desaturation were counted manually by one of the investigators (JL), who was blinded regarding the position during the recordings". Low possibility of data analysis bias was noted as well, because "pneumograms were analyzed using a Pediatric Diagnostic Service computer program".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data on only 10 of 14 infants regarding duration of spells of apnoea and desaturation were reported. However, data for all other outcomes measured in the study were available on all participants with no missing data.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the study protocol.
Other bias	Unclear risk	• Carry-over of treatment effect - The order in which interventions were administered may have affected the outcome. However, a 12-hour "wash-out" period between interventions was reported (low risk). - Even though infants were assigned to the supine position, infants were nursed prone for 1 hour after feeds to 'prevent aspiration'. This may have influenced the outcome measure of apnoea during this period because both the supine group and the prone group were in the prone position 1 hour post feed (high risk).

Jenni 1997

Methods	Randomised controlled cross-over trial
Participants	Participants: 12 preterm infants (6 males and 6 females) with a history of recurrent apnoea and bradycardic and hypoxaemic events but with no other conditions (otherwise healthy) Nine infants were treated with aminophylline (dosage not mentioned) for at least 3 days but had a serum concentration within the normal therapeutic range (33-76 micromol/L). Maintenance dose (6 mg/kg) was not changed during the trial. Eight infants received supplemental oxygen (inspired oxygen fraction range 23%-32%). Infants with heart disease, intracranial haemorrhage, anaemia or infection were excluded. Mean gestational age at birth: 28 weeks (range 26-31 weeks) Postnatal age: 6-38 days

Jenni 1997 *(Continued)*

	Mean birth weight: 1145 grams (range 815-1450 grams)
Interventions	Prone horizontal (flat) vs prone elevated (15 degree tilt) head positions Total study time was 48 hours. Each infant remained for a total of 24 hours in each of the 2 compared positions - horizontal position (HP, prone, 0 degrees) and horizontal head elevated tilt position (HETP, prone, 15 degrees). Position was changed every 6 hours on the first day. On the second day, the sequence of tilt and horizontal position was reversed. During the study, each infant was nursed in an incubator. The inspired oxygen fraction and air temperature were maintained at constant levels and were noted every 2 hours. Gastric residue was documented every 2 hours. Breathing movements were recorded by thoracic impedance pneumography, in which skin electrodes were attached to both sides of the chest; a Hellige Servomed (Freiburg, Germany) respiration monitor was used. Heart rate was monitored by a Hellige Servomed ECG monitor. Oxygen saturation was recorded by pulse oximetry (Nellcor N-200; Pleasanton, California, USA) with the sensor placed on the right foot of each infant.
Outcomes	• Episodes of isolated bradycardia, defined as a decrease in heart rate to < 90 beats per minute • Episodes of isolated hypoxaemia, defined as a drop in arterial oxygen saturation to < 80% • Episodes of mixed events, defined as a decrease in oxygen saturation to < 80% and a decrease in heart rate to < 90 beats per minute (Episodes of apnoea were not recorded.)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data were reported on how randomisation was performed.
Allocation concealment (selection bias)	High risk	Infants were 'randomly' assigned to allocated positions and then were shifted to the other position every 6 hours. Thus, it would be easy to trace back the initial allocation position of each infant.
Blinding of participants and personnel (performance bias) All outcomes	High risk	High possibility of performance bias was due to knowledge of allocated interventions by personnel attending the infants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low possibility of detection bias was due to blinding of allocated interventions by outcome assessors. "Isolated and mixed events were counted without the knowledge of the position of the infant".

Jenni 1997 *(Continued)*

		Low possibility of data analysis bias was noted as well because "The data were analysed from masked files, and then, the results were combined with the allocated body position".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, and researchers reported no losses to follow-up, no treatment withdrawals and no trial group changes. Data are available for all 12 participants enrolled in the study.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the study protocol.
Other bias	High risk	Carry-over of treatment effect The order in which interventions were administered may have affected the outcome, especially because no "wash-out" period between interventions was reported.

Keene 2000

Methods	Randomised controlled cross-over trial
Participants	Participants: 22 preterm infants (10 males and 12 females) with symptomatic apnoea and bradycardia but with no other conditions (otherwise healthy) Infants were not studied for the first 24 hours after extubation or discontinuation of CPAP. Sixteen infants were receiving methylxanthines and 4 were receiving both methylxanthines and doxapram for treatment of apnoea. Sixteen infants were treated for RDS with mechanical ventilation and surfactant administration. Thirteen infants were receiving supplemental oxygen during the study. Infants with any condition that prevented them from being placed in the prone or supine position (e.g. gastroschisis and meningomyelocoele, respectively) were excluded from the study. Mean gestational age: 26.9 ± 1.8 weeks (range 24-30 weeks) Mean postconceptual age: 31.9 ± 3 weeks (range 28-36 weeks) Mean birth weight: 865 ± 235 grams (range 500-1331 grams)
Interventions	Supine vs prone position Each infant was studied in 6-hour blocks in both prone and supine positions for a continuous 24-hour period. The initial position was randomly assigned, and prone and supine positions were subsequently alternated. Infants remained in their allocated positions throughout the 6-hour designated period, except during times of assessment and feeding within the period. Infants in the prone position had their face tilted to the side, whereas those in the supine position were allowed to assume a natural position. Heart rate and respiration were monitored with standard chest electrodes connected to a cardiorespiratory monitor that had event-recording capability (Edentec Assurance 2000; Edentec, Minneapolis, Minnesota, USA).

Keene 2000 *(Continued)*

	Oxygen saturation was measured with a pulse oximeter (Nellcor 200; Nellcor, Hayward, California, USA), which was connected to the event-recording monitor.
Outcomes	• Episodes of apnoea, measured as the number of cessations of breathing lasting ≥ 10 seconds and classified by severity as: - Mild (< 15 seconds); or - Clinically significant (≥ 15 seconds). • Episodes of bradycardia, defined as a drop in heart rate to < 100 beats per minute and classified by severity as: - Mild (≥ 90 beats per minute); or - Clinically significant (< 90 beats per minute). • Episodes of oxygen desaturation, defined as a drop in arterial oxygen saturation to < 90% and classified by severity as: - Mild (≥ 80%); or - Clinically significant (< 80%).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data reported how randomisation was performed.
Allocation concealment (selection bias)	High risk	Infants were 'randomly' assigned to an allocated position, then were shifted to the other position every 6 hours. Thus, it would be easy to trace back the initial allocation position of each infant.
Blinding of participants and personnel (performance bias) All outcomes	High risk	High possibility of performance bias was due to knowledge of allocated interventions by personnel attending the infants.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Possibility of detection bias was low because all instruments used to measure cardiorespiratory parameters were equipped with intrinsic event-recording monitors, which excluded the need for personnel to collect data. However, no information was reported on whether any blinding occurred at the data analysis stage.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was reported on missing outcome data or loss to follow-up and how these were handled. The paper does not mention or tabulate how many or if all enrolled infants (22) had data provided.
Selective reporting (reporting bias)	Unclear risk	We were unable to obtain the study protocol.
Other bias	High risk	Carry-over of treatment effect

Keene 2000 *(Continued)*	
	The order in which interventions were administered may have affected the outcome, especially as no "wash-out" period between interventions was provided.

CPAP: continuous positive airway pressure.
ECG: electrocardiogram.
HETP: head elevated tilt position
RDS: respiratory distress syndrome.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhat 2003	Supine and prone positions were randomised, and effects of body position on oxygen saturation and respiratory mechanics (primary outcomes) were measured in oxygen- and non-oxygen-dependent preterm infants before discharge. Episodes of apnoea and bradycardia were not documented.
Dellagrammaticas 1991	Body positions were not randomised.
Heimann 2010	Body positions were not randomised.
Kurlak 1994	Means or standard deviations were not reported. We were unable to obtain additional data from the study author.
Nimavat 2006	This study was published as abstract only. Means or standard deviations were not reported. Study authors were contacted, but we were unable to obtain additional data.
Pichler 2001	Primary outcomes were not relevant.
Reher 2008	Infants were receiving nasal continuous positive airway pressure (CPAP).

Characteristics of studies awaiting assessment *[ordered by study ID]*

Yaming 2015

Methods	Randomised controlled trial
Participants	Preterm infants
Interventions	15-degree head elevated prone position vs 3-stair position
Outcomes	Heart rate Respiratory rate Oxygen saturation
Notes	In Chinese

DATA AND ANALYSES

Comparison 1. Supine versus prone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	2	72	Mean Difference (IV, Fixed, 95% CI)	1.09 [-0.65, 2.82]
2 Episodes of oxygen desaturation	1	44	Mean Difference (IV, Fixed, 95% CI)	0.80 [-3.19, 4.79]
3 Episodes of bradycardia	2	72	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-3.20, 2.94]

Analysis 1.1. Comparison 1 Supine versus prone, Outcome 1 Episodes of apnoea.

Study or subgroup	Supine N	Supine Mean(SD)	Prone N	Prone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heimler 1992	14	2.3 (3.7)	14	0.4 (0.8)		75.41%	1.9[-0.1,3.9]
Keene 2000	22	4.1 (4.1)	22	5.5 (7.3)		24.59%	-1.4[-4.9,2.1]
Total ***	**36**		**36**			**100%**	**1.09[-0.65,2.82]**
Heterogeneity: Tau^2=0; Chi^2=2.58, df=1(P=0.11); I^2=61.2%							
Test for overall effect: Z=1.23(P=0.22)							

Favours Supine — Favours Prone

Analysis 1.2. Comparison 1 Supine versus prone, Outcome 2 Episodes of oxygen desaturation.

Study or subgroup	Supine N	Supine Mean(SD)	Prone N	Prone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Keene 2000	22	7.1 (5.9)	22	6.3 (7.5)		100%	0.8[-3.19,4.79]
Total ***	**22**		**22**			**100%**	**0.8[-3.19,4.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.39(P=0.69)							

Favours Supine — Favours Prone

Analysis 1.3. Comparison 1 Supine versus prone, Outcome 3 Episodes of bradycardia.

Study or subgroup	Supine N	Supine Mean(SD)	Prone N	Prone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heimler 1992	14	3.4 (3.7)	14	3.8 (5.6)		75.61%	-0.4[-3.93,3.13]
Keene 2000	22	9.7 (12)	22	9 (8.8)		24.39%	0.7[-5.52,6.92]
Total ***	**36**		**36**			**100%**	**-0.13[-3.2,2.94]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.76); I^2=0%							
Test for overall effect: Z=0.08(P=0.93)							

Favours Supine — Favours Prone

Comparison 2. Prone horizontal versus right lateral horizontal

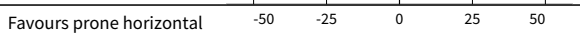
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	2	130	Mean Difference (IV, Fixed, 95% CI)	0.48 [-0.19, 1.15]
2 Episodes of oxygen desaturation	1	88	Mean Difference (IV, Fixed, 95% CI)	-1.86 [-4.29, 0.56]
3 Episodes of severe apnoea	1	88	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.45, 0.54]
4 Episodes of bradycardia	1	88	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-2.41, 1.23]
5 Episodes of severe bradycardia	1	88	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-1.02, 0.39]

Analysis 2.1. Comparison 2 Prone horizontal versus right lateral horizontal, Outcome 1 Episodes of apnoea.

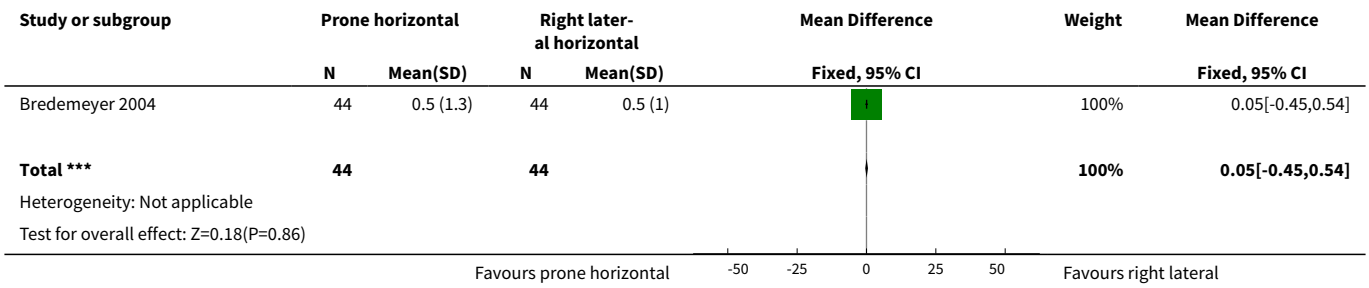
Study or subgroup	Prone horizontal		Right lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 1992	21	19.2 (14.7)	21	18.7 (11.3)		0.72%	0.52[-7.39,8.43]
Bredemeyer 2004	44	1 (1.9)	44	0.6 (1.2)		99.28%	0.48[-0.2,1.15]
Total ***	**65**		**65**			**100%**	**0.48[-0.19,1.15]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%							
Test for overall effect: Z=1.4(P=0.16)							

Analysis 2.2. Comparison 2 Prone horizontal versus right lateral horizontal, Outcome 2 Episodes of oxygen desaturation.

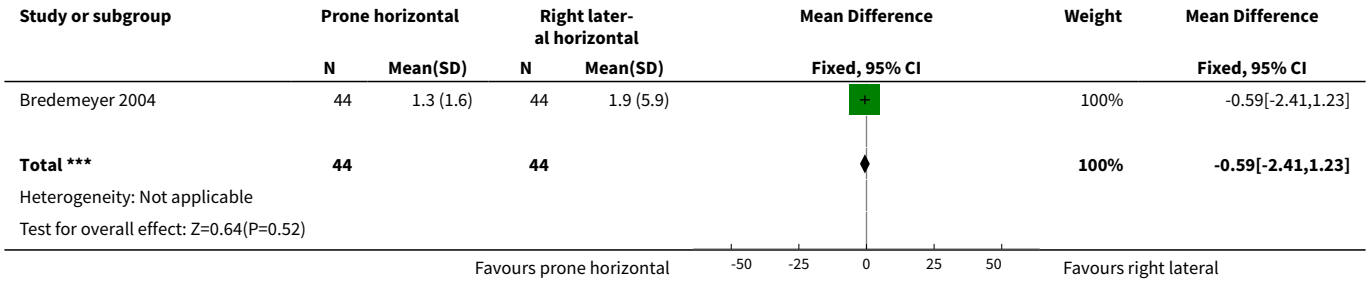
Study or subgroup	Prone horizontal		Right lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	44	4.1 (4.4)	44	5.9 (6.9)		100%	-1.86[-4.29,0.56]
Total ***	**44**		**44**			**100%**	**-1.86[-4.29,0.56]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=1.51(P=0.13)							



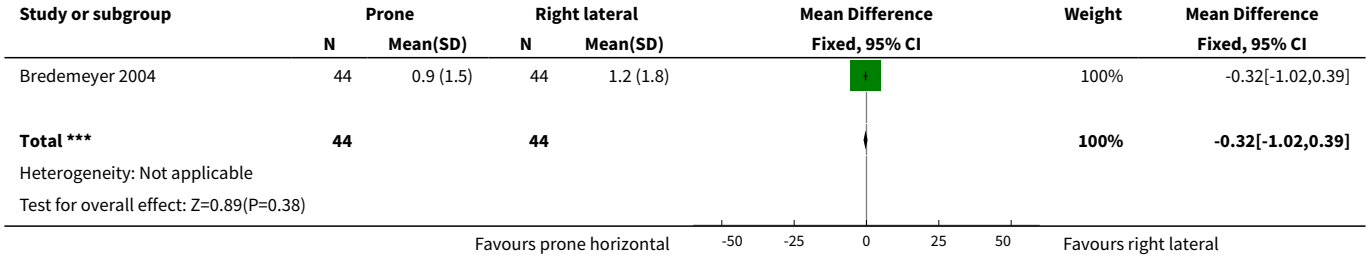
Analysis 2.3. Comparison 2 Prone horizontal versus right lateral horizontal, Outcome 3 Episodes of severe apnoea.



Analysis 2.4. Comparison 2 Prone horizontal versus right lateral horizontal, Outcome 4 Episodes of bradycardia.



Analysis 2.5. Comparison 2 Prone horizontal versus right lateral horizontal, Outcome 5 Episodes of severe bradycardia.



Comparison 3. Prone horizontal versus left lateral horizontal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	2	131	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.75, 1.15]
2 Episodes of oxygen desaturation	1	89	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-3.81, 0.92]
3 Episodes of severe apnoea	1	89	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.38, 0.60]
4 Episodes of bradycardia	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.94, 0.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Episodes of severe bradycardia	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.94, 0.49]

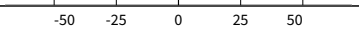
Analysis 3.1. Comparison 3 Prone horizontal versus left lateral horizontal, Outcome 1 Episodes of apnoea.

Study or subgroup	Prone horizontal		Left lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 1992	21	19.2 (14.7)	21	19 (11.3)		1.43%	0.19[-7.72,8.1]
Bredemeyer 2004	44	1 (1.9)	45	0.8 (2.6)		98.57%	0.2[-0.75,1.16]
Total ***	**65**		**66**			**100%**	**0.2[-0.75,1.15]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=0.42(P=0.68)							

Favours prone — Favours left lateral

Analysis 3.2. Comparison 3 Prone horizontal versus left lateral horizontal, Outcome 2 Episodes of oxygen desaturation.

Study or subgroup	Prone horizontal		Left lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	44	4.1 (4.4)	45	5.5 (6.8)		100%	-1.44[-3.81,0.92]
Total ***	**44**		**45**			**100%**	**-1.44[-3.81,0.92]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.2(P=0.23)							



Favours prone — Favours left lateral

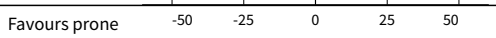
Analysis 3.3. Comparison 3 Prone horizontal versus left lateral horizontal, Outcome 3 Episodes of severe apnoea.

Study or subgroup	Prone horizontal		Left lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	44	0.6 (1.3)	45	0.4 (1)		100%	0.11[-0.38,0.6]
Total ***	**44**		**45**			**100%**	**0.11[-0.38,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.44(P=0.66)							

Favours prone — Favours left lateral

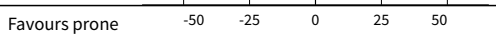
Analysis 3.4. Comparison 3 Prone horizontal versus left lateral horizontal, Outcome 4 Episodes of bradycardia.

Study or subgroup	Prone horizontal		Left lateral horizontal		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	44	1.3 (1.6)	45	1.5 (2.1)		100%	-0.17[-0.94,0.6]
Total ***	**44**		**45**			**100%**	**-0.17[-0.94,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.43(P=0.66)							



Analysis 3.5. Comparison 3 Prone horizontal versus left lateral horizontal, Outcome 5 Episodes of severe bradycardia.

Study or subgroup	Prone		Left lateral		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	44	0.9 (1.5)	45	1.1 (1.9)		100%	-0.22[-0.94,0.49]
Total ***	**44**		**45**			**100%**	**-0.22[-0.94,0.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.62(P=0.54)							

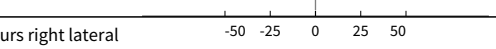


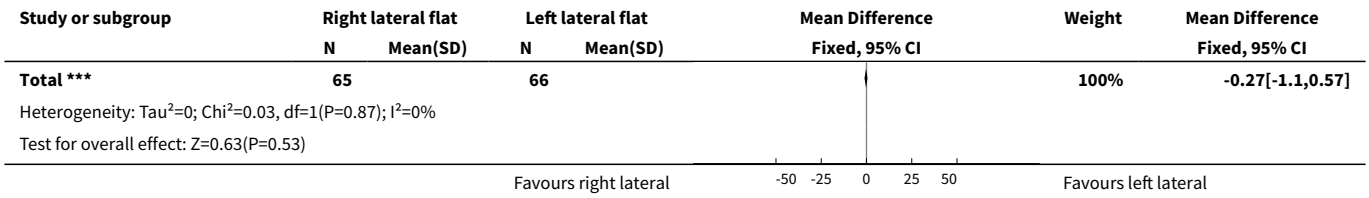
Comparison 4. Right lateral versus left lateral

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	2	131	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-1.10, 0.57]
2 Episodes of oxygen desaturation	1	89	Mean Difference (IV, Fixed, 95% CI)	0.42 [-2.42, 3.26]
3 Episodes of severe apnoea	1	89	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.40, 0.42]
4 Episodes of bradycardia	1	89	Mean Difference (IV, Fixed, 95% CI)	0.42 [-1.43, 2.27]
5 Episodes of severe bradycardia	1	89	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.68, 0.87]

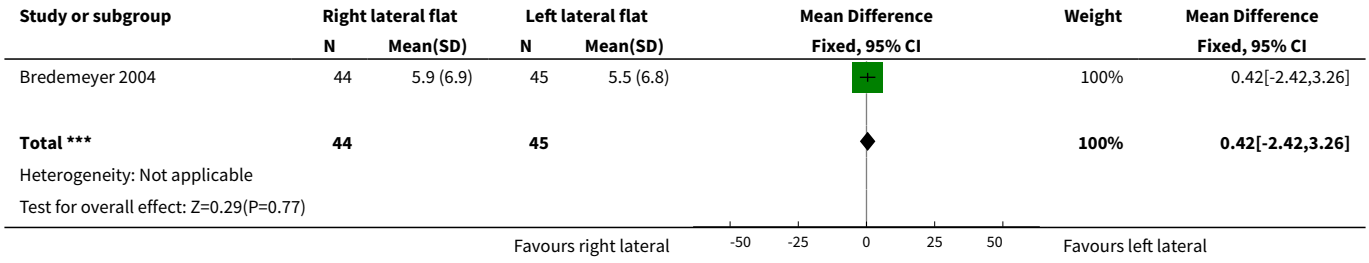
Analysis 4.1. Comparison 4 Right lateral versus left lateral, Outcome 1 Episodes of apnoea.

Study or subgroup	Right lateral flat		Left lateral flat		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 1992	21	19 (11.3)	21	18.7 (12.3)		1.36%	0.33[-6.82,7.48]
Bredemeyer 2004	44	0.6 (1.2)	45	0.8 (2.6)		98.64%	-0.28[-1.11,0.56]

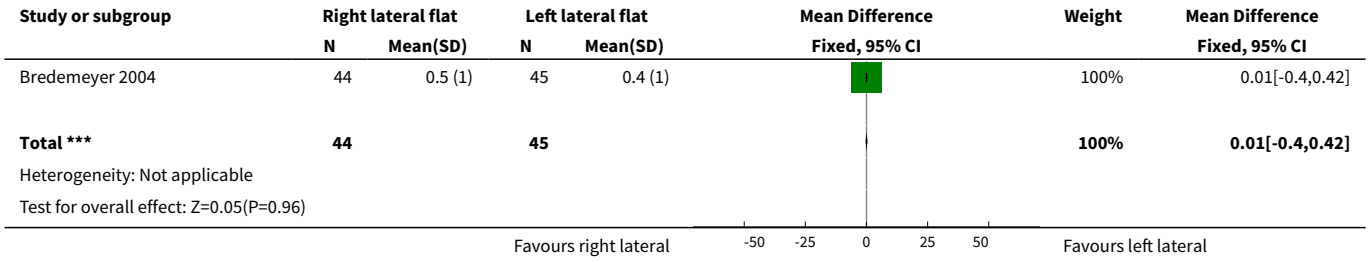




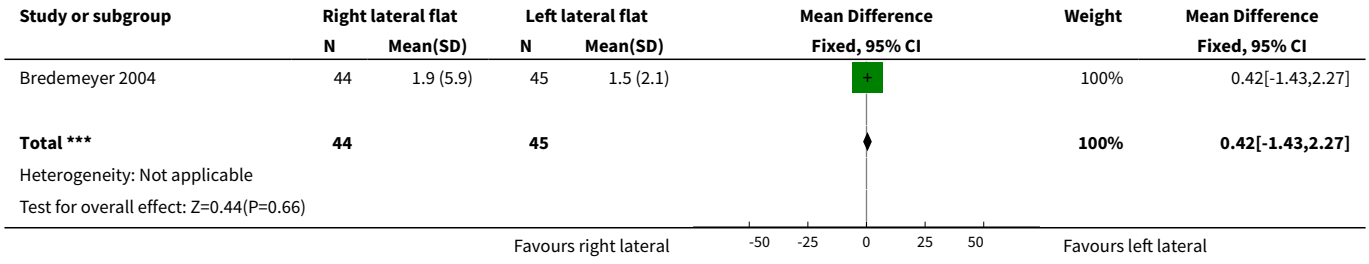
Analysis 4.2. Comparison 4 Right lateral versus left lateral, Outcome 2 Episodes of oxygen desaturation.



Analysis 4.3. Comparison 4 Right lateral versus left lateral, Outcome 3 Episodes of severe apnoea.



Analysis 4.4. Comparison 4 Right lateral versus left lateral, Outcome 4 Episodes of bradycardia.



Analysis 4.5. Comparison 4 Right lateral versus left lateral, Outcome 5 Episodes of severe bradycardia.

Study or subgroup	Right lateral N	Right lateral Mean(SD)	Left lateral N	Left lateral Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	1.2 (1.8)	45	1.1 (1.9)		100%	0.09[-0.68,0.87]
Total ***	**44**		**45**			**100%**	**0.09[-0.68,0.87]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.24(P=0.81)							

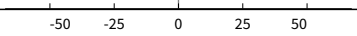
Favours right lateral — Favours left lateral

Comparison 5. Prone horizontal versus prone head elevated

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	2	129	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-1.09, 0.73]
2 Episodes of oxygen desaturation	2	111	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-2.81, 1.56]
3 Episodes of severe apnoea	1	87	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.83, 0.35]
4 Episodes of bradycardia	2	111	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-1.03, 0.74]
5 Episodes of severe bradycardia	2	111	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-1.15, 0.59]

Analysis 5.1. Comparison 5 Prone horizontal versus prone head elevated, Outcome 1 Episodes of apnoea.

Study or subgroup	Prone horizontal N	Prone horizontal Mean(SD)	Prone elevated N	Prone elevated Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 1992	21	19.2 (14.7)	21	18.6 (13.7)		1.12%	0.62[-7.97,9.21]
Bredemeyer 2004	44	1 (1.9)	43	1.2 (2.4)		98.88%	-0.19[-1.1,0.73]
Total ***	**65**		**64**			**100%**	**-0.18[-1.09,0.73]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%							
Test for overall effect: Z=0.38(P=0.7)							

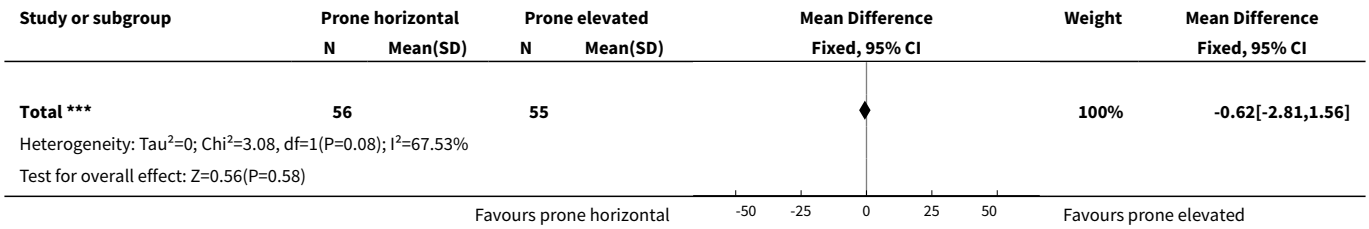


Favours prone horizontal — Favours prone elevated

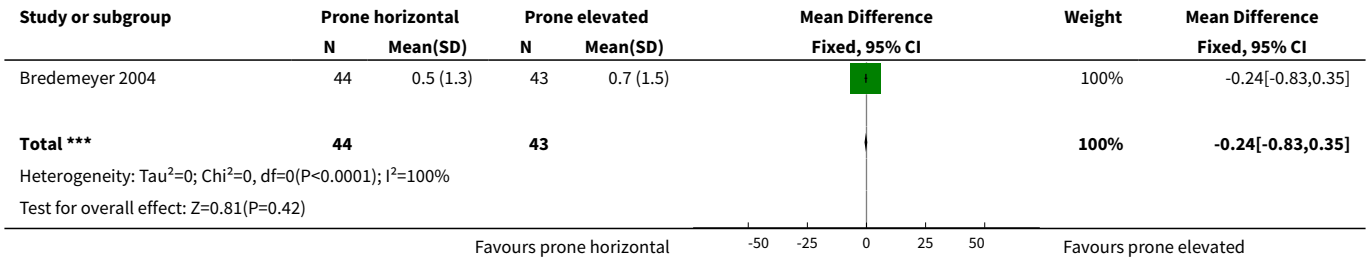
Analysis 5.2. Comparison 5 Prone horizontal versus prone head elevated, Outcome 2 Episodes of oxygen desaturation.

Study or subgroup	Prone horizontal N	Prone horizontal Mean(SD)	Prone elevated N	Prone elevated Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	4.1 (4.4)	43	5 (6)		97.56%	-0.93[-3.15,1.28]
Jenni 1997	12	24.2 (19.9)	12	12.5 (14.7)		2.44%	11.75[-2.24,25.74]

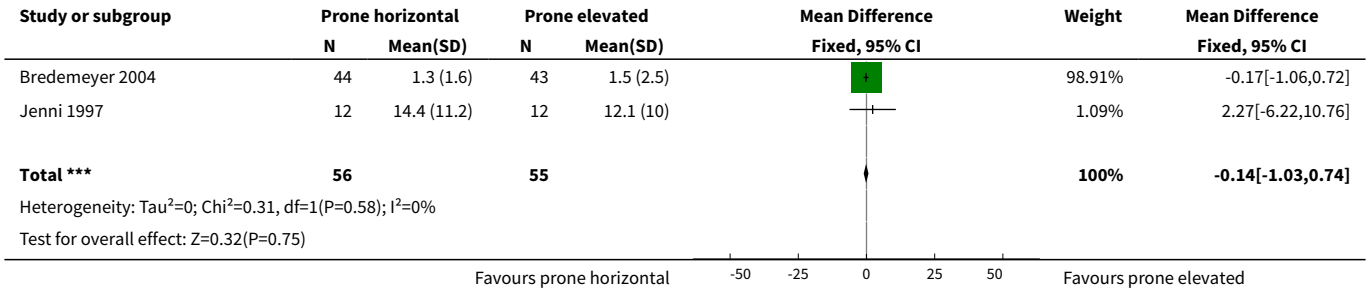
Favours prone horizontal — Favours prone elevated



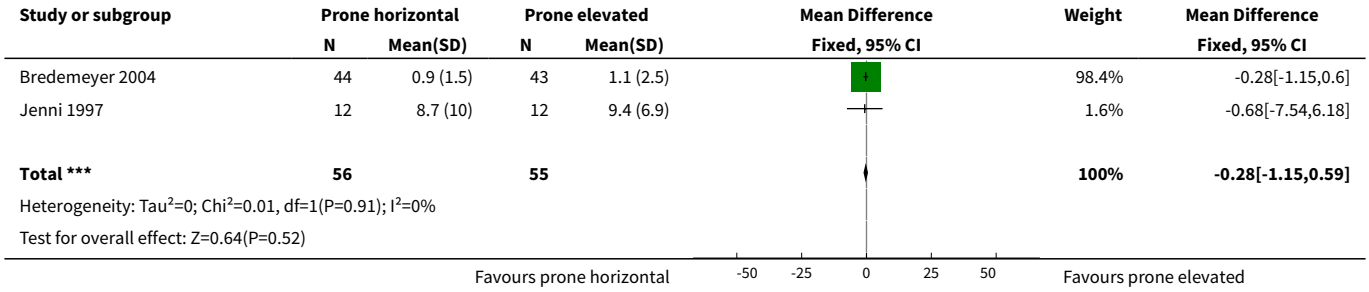
Analysis 5.3. Comparison 5 Prone horizontal versus prone head elevated, Outcome 3 Episodes of severe apnoea.



Analysis 5.4. Comparison 5 Prone horizontal versus prone head elevated, Outcome 4 Episodes of bradycardia.



Analysis 5.5. Comparison 5 Prone horizontal versus prone head elevated, Outcome 5 Episodes of severe bradycardia.

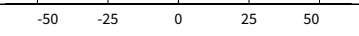


Comparison 6. Right lateral horizontal versus right lateral elevated

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episides of apnoea	1	86	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-2.26, 0.69]
2 Episodes of oxygen desaturation	1	86	Mean Difference (IV, Fixed, 95% CI)	0.03 [-3.06, 3.11]
3 Episodes of severe apnoea	1	86	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.69, 0.41]
4 Episodes of bradycardia	1	86	Mean Difference (IV, Fixed, 95% CI)	0.34 [-1.54, 2.22]
5 Episodes of severe bradycardia	1	86	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.25, 1.46]

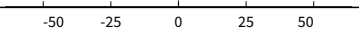
Analysis 6.1. Comparison 6 Right lateral horizontal versus right lateral elevated, Outcome 1 Episides of apnoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	0.6 (1.2)	42	1.4 (4.7)		100%	-0.79[-2.26,0.69]
Total ***	**44**		**42**			**100%**	**-0.79[-2.26,0.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.05(P=0.29)							



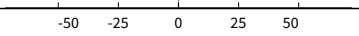
Analysis 6.2. Comparison 6 Right lateral horizontal versus right lateral elevated, Outcome 2 Episodes of oxygen desaturation.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	5.9 (6.9)	42	5.9 (7.6)		100%	0.03[-3.06,3.11]
Total ***	**44**		**42**			**100%**	**0.03[-3.06,3.11]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.02(P=0.99)							

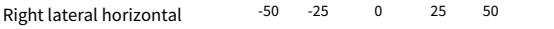


Analysis 6.3. Comparison 6 Right lateral horizontal versus right lateral elevated, Outcome 3 Episodes of severe apnoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	0.5 (1)	42	0.6 (1.5)		100%	-0.14[-0.69,0.41]

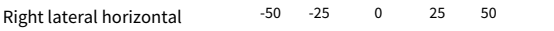


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**44**		**42**			**100%**	**-0.14[-0.69,0.41]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.5(P=0.62)							



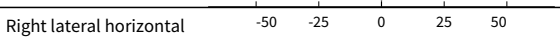
Analysis 6.4. Comparison 6 Right lateral horizontal versus right lateral elevated, Outcome 4 Episodes of bradycardia.

Study or subgroup	Right lateral horizontal N	Right lateral horizontal Mean(SD)	Right lateral elevated N	Right lateral elevated Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	1.9 (5.9)	42	1.6 (2.3)		100%	0.34[-1.54,2.22]
Total ***	**44**		**42**			**100%**	**0.34[-1.54,2.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.72)							



Analysis 6.5. Comparison 6 Right lateral horizontal versus right lateral elevated, Outcome 5 Episodes of severe bradycardia.

Study or subgroup	Right lateral horizontal N	Right lateral horizontal Mean(SD)	Right lateral elevated N	Right lateral elevated Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	44	1.8 (1.8)	42	1.2 (2.2)		100%	0.6[-0.25,1.46]
Total ***	**44**		**42**			**100%**	**0.6[-0.25,1.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.38(P=0.17)							



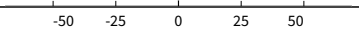
Comparison 7. Left lateral horizontal versus left lateral elevated

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of apnoea	1	87	Mean Difference (IV, Fixed, 95% CI)	0.46 [-0.34, 1.26]
2 Episodes of oxygen desaturation	1	87	Mean Difference (IV, Fixed, 95% CI)	0.63 [-2.09, 3.35]
3 Episodes of severe apnoea	1	87	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.18, 0.54]
4 Episodes of bradycardia	1	87	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.71, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Episodes of severe bradycardia	1	87	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.93, 0.58]

Analysis 7.1. Comparison 7 Left lateral horizontal versus left lateral elevated, Outcome 1 Episodes of apnoea.

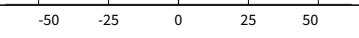
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	45	0.8 (2.6)	42	0.4 (0.8)		100%	0.46[-0.34,1.26]
Total ***	**45**		**42**			**100%**	**0.46[-0.34,1.26]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.13(P=0.26)							



Left lateral horizontal — Left lateral elevated

Analysis 7.2. Comparison 7 Left lateral horizontal versus left lateral elevated, Outcome 2 Episodes of oxygen desaturation.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	45	5.5 (6.8)	42	4.9 (6.2)		100%	0.63[-2.09,3.35]
Total ***	**45**		**42**			**100%**	**0.63[-2.09,3.35]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.45(P=0.65)							



Left lateral horizontal — Left lateral elevated

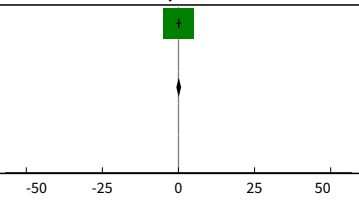
Analysis 7.3. Comparison 7 Left lateral horizontal versus left lateral elevated, Outcome 3 Episodes of severe apnoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bredemeyer 2004	45	0.4 (1)	42	0.3 (0.7)		100%	0.18[-0.18,0.54]
Total ***	**45**		**42**			**100%**	**0.18[-0.18,0.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1(P=0.32)							

Left lateral horizontal — Left lateral elevated

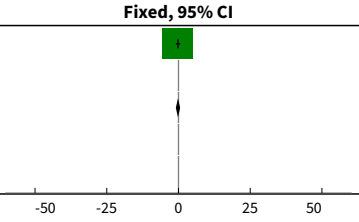
Analysis 7.4. Comparison 7 Left lateral horizontal versus left lateral elevated, Outcome 4 Episodes of bradycardia.

Study or subgroup	Left lateral horizontal		Left lateral elevated		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	45	1.5 (2.1)	42	1.4 (1.7)		100%	0.08[-0.71,0.88]
Total ***	**45**		**42**			**100%**	**0.08[-0.71,0.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.21(P=0.84)							



Analysis 7.5. Comparison 7 Left lateral horizontal versus left lateral elevated, Outcome 5 Episodes of severe bradycardia.

Study or subgroup	Left lateral horizontal		Left lateral elevated		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bredemeyer 2004	45	1.1 (1.9)	42	1.3 (1.7)		100%	-0.17[-0.93,0.58]
Total ***	**45**		**42**			**100%**	**-0.17[-0.93,0.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.45(P=0.65)							



APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

Random sequence generation (checking for possible selection bias)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the risk of bias methods as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the risk of bias methods as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth); or
- unclear risk.

Blinding (checking for possible performance bias)

For each included study, we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged the study to be at low risk of bias if it was blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes and classes of outcomes. We assessed the risk of bias methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel; or
- adequate, inadequate or unclear for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs and protocol deviations)

For each included study and for each outcome or class of outcome, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses. We assessed the risk of bias methods as:

- adequate (less than 20% missing data);
- inadequate; or
- unclear.

Selective reporting bias

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the risk of bias methods as:

- low risk (when it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
- high risk (when not all of the study's prespecified outcomes had been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study did not include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

Other sources of bias

For each included study, we described any important concerns that we had about other possible sources of bias (e.g. early termination of trial due to data-dependant process, extreme baseline imbalance). We assessed whether each study was free of other problems that could put it at risk of bias. We assessed other sources of bias as:

- low risk;
- high risk; or
- unclear.

Overall risk of bias

We made judgements as to whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to overall risk of bias, we assessed the likely magnitude and direction of the bias, and whether we considered it likely to have an impact on the findings.

WHAT'S NEW

Date	Event	Description
6 February 2017	Amended	Added external source of support.

HISTORY

Protocol first published: Issue 4, 2004
Review first published: Issue 6, 2012

Date	Event	Description
14 November 2016	New search has been performed	Search was updated. 'Summary of findings' tables and GRADE recommendations were added.
14 November 2016	New citation required but conclusions have not changed	Updated search identified no new studies.
29 October 2008	Amended	Review was converted to new review format.

CONTRIBUTIONS OF AUTHORS

Rami A. Ballout: Title and Abstract screening, full-text acquisition and screening, data extraction (characteristics of included studies and risk of bias assessment), co-ordination of the review between investigators (Lina Badr and Jann Foster) and the Cochrane Neonatal Review Group, update of included references, drafting and finalisation of the review.

Jann P. Foster: Meta-analyses, Summary of findings tables, drafting and finalisation of the review.

Lara A. Kahale: Methodological guidance on the conduct of the update, drafting the Methods section.

Lina Badr: Title and Abstract screening, full-text screening, expert insight on neonatal care and implications of findings for future research, update of included references, drafting and finalisation of the review.

All review authors have read and approved the final manuscript.

DECLARATIONS OF INTEREST

The review authors have declared no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

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- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added Methods details and plans for Summary of findings tables and GRADE recommendations, which were not included in the original protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Apnea [*therapy]; Bradycardia [therapy]; Infant, Premature; Infant, Premature, Diseases [*therapy]; Oxygen Consumption; Patient Positioning [*methods]; Posture [physiology]; Randomized Controlled Trials as Topic; Respiration

MeSH check words

Humans; Infant, Newborn